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EXPERIMENTAL NEPHROTIC EDEMA

LOUIS LEITER, M D

WITH THE TECHNICAL ASSISTANCE OF

M ELEANOR BLISH, S B, AND DOROTHY R GASTON, P H D

CHICAGO

Richard Bright¹ was well aware of the effects of prolonged albuminuria on the serum proteins, because he actually obtained quantitative analytic data with the help of friends who were chemists. He believed that the thin, watery plasma filtered out into the tissue spaces readily, thus producing dropsy. It is obvious that he considered renal edema as uniform in type and in causation. For almost a hundred years clinicians and physiologists failed to distinguish between the different forms of dropsy occurring in Bright's disease and sought to explain them all on a single basis. The experimental work on edema reflected accurately the prevailing clinical theories. Thus Bright's theory of hydremia as the cause of edema was put to the experimental test by Cohnheim and Lichtheim² and found wanting. Similarly, the rôle of oliguria and hydremic plethora defended by Bartels³ and Grainger Stewart⁴ was more or less definitely disposed of by the classic experiments of Cohnheim and Lichtheim,² Magnus⁵ and others. There remained only one unassailed, and apparently unassailable, universal theory of renal edema—Senator's⁶ conception of increased permeability of the capillaries secondary to toxic injury, expressing itself in the glomerular capillaries by albuminuria and anatomic renal disease, and in the cutaneous and serous capillaries by edema. The postscarlatinal nephritis with edema was the keystone of this theory. There was ample experimental support for the association of edema with capillary injury. The work of Cohnheim and Lichtheim,² Magnus,⁵ Richter,⁷ Georg-

¹ Submitted for publication, Sept. 14, 1930.

² From the Lasker Foundation for Medical Research and the Department of Medicine of the University of Chicago.

1 Bright, Richard. Reports of Medical Cases, London, 1827, vol. 1.

2 Cohnheim, J., and Lichtheim, L. Virchows Arch f path Anat **69** 106 1877.

3 Bartels, C. Handbuch der speziellen Pathologie und Therapie, Leipzig, F C W Vogel, 1875, vol. 9.

4 Stewart, Grainger F. Practical Treatise of Bright's Disease of the Kidneys, Edinburgh, 1871.

5 Magnus, R. Arch exper Path u Pharmakol **42** 250, 1899.

6 Senator, H. Berl klin Wchnschr **32** 165, 1895.

7 Richter, P F. Berl klin Wchnschr **42** 384, 1905, Deutsche med Wchnschr **36** 1737, 1910.

opulos,⁸ Heineke and Meyerstein⁹ and Pearce¹⁰ clearly demonstrated the dependence of edema on damage to the capillaries by such irritants as heat, iodine, arsenic, chloroform, metabolic products in a dying animal, snake venoms and especially uranium nitrate. The analogy between the experimental edemas and the dropsy of Bright's disease seemed very close.

It is a curious fact that it did not seem to occur to any one of the numerous investigators of this problem to compare human and experimental edema fluids in a quantitative manner, although scattered analyses were published on one or the other separately. This was an important and far-reaching omission, because it delayed the proper clinical recognition of Starling's¹¹ contributions to the physiology of fluid exchange for about twenty years. Starling¹² had shown in 1896 that the colloid osmotic pressure of the plasma proteins was a measurable force and one quantitatively adequate to effect the reabsorption of physiologic tissue fluids into the vascular capillaries. Necessary corollaries of his theory were the relative impermeability of the normal peripheral capillaries to the plasma proteins and a low concentration of protein in normal subcutaneous tissue fluids. Therefore, when Epstein¹³ demonstrated by systematic quantitative analysis of edema fluids in patients with Bright's disease that in some cases the protein content was extremely low, and when he¹⁴ later was the first to apply Starling's concept by explaining the edema of nephrotic Bright's disease as the result of marked albuminuria and decreased concentration of plasma protein the older theory of increased permeability collapsed for nephrotic renal edema, because, with the capillaries injured and more permeable, the edema fluid should have a considerably higher protein content than was actually found. One began, therefore, to distinguish between nephrotic, low protein edema and nephritic, high protein edema.¹⁵ The former was a true transudate or ultrafiltrate of the plasma, something approximating the cerebrospinal fluid or the aqueous humor, while the latter was much more like an inflammatory exudate.

This distinction between clinical edema fluids, when applied to the experimental edemas produced up to 1917, leads to the obvious con-

8 Georgopulos. *Ztschr f klin Med* **60** 411, 1906

9 Heineke, A., and Meyerstein, W. *Deutsches Arch f klin Med* **90** 101, 1907

10 Pearce, R. M. *The Production of Edemas, Arch Int Med* **3** 422 (June) 1909

11 Starling, E. H. *Lancet* **1** 1267, 1331 and 1407, 1896

12 Starling, E. H. *J Physiol* **19** 312, 1896

13 Epstein, A. A. *J Exper Med* **20** 334, 1914

14 Epstein, A. A. *Am J M Sc* **154** 638, 1917

15 Beckmann, K. *Deutsches Arch f klin Med* **135** 39, 1921

clusion that all of the earlier experimental edemas were of the exudative type, rich in protein and undoubtedly based on more or less extensive capillary damage with resulting increased permeability to the plasma proteins. Therefore, no one had really produced a nephrotic edema.

THE PROBLEM

The problem was relatively simple as it presented itself in 1925. At the suggestion of Dr. D. D. Van Slyke, work was begun on dogs with the specific aim of producing, by means of experimental hypoproteinemia, an edema fluid low in protein. If renal, cardiac and capillary damage could be excluded as significant factors in this edema, the Starling-Epstein theory of nephrotic edema would find its first direct experimental confirmation. It was recognized at the outset that an adequate supply of salt and water was an important accessory factor for, regardless of the general tendency to edema as the result of the experimental procedure, little transudate could be formed without freely available salt and water. The most important single feature of this work was considered to be the determination of the protein content of the experimental effusions. Without such quantitative data no conclusions could safely be drawn as to the pathogenesis of the experimental edema.

Since the first preliminary publication of our results¹⁶ the problem has expanded in various directions, and at present involves the question of experimental nephrosis,¹⁷ that is, the whole nephrotic syndrome, the renal lesions supposed to result from plasmapheresis¹⁸ and other phases on which no final statements can yet be made. It may be said, however, that the original simpler problem has been solved with a reasonable degree of certainty. There is no doubt now as to the relationship between low plasma proteins and a nephrotic type of edema in dogs. That the same situation may hold true for rabbits was suggested earlier by Fishberg and Fishberg,¹⁹ but they observed no gross edema, and therefore had no material available for analysis.

METHODS

Physiologic—Dogs that weighed between 10 and 15 Kg. were ordinarily used. They were kept on the standard diet of a mixture of bread and meat without exact quantitative control. Water was allowed ad libitum. The animals were bled

16 Leiter, L. Proc Soc Exper Biol & Med **26**:173, 1928

17 Barker, M. H., and Kirk, E. J. Experimental Edema (Nephrosis) in Dogs in Relation to Edema of Renal Origin in Patients, Arch Int Med **45** 319 (March) 1930

18 Barker, M. H. Proc Soc Exper Biol & Med **27** 608, 1930. Barker and Kirk (footnote 17)

19 Fishberg, E. H., and Fishberg, A. M. Proc Soc Exper Biol & Med **25** 296, 1928

usually from the heart, by suction through a 3 inch gage 16 needle connected with a 250 cc pyrex centrifuge bottle containing 20 cc of 5 per cent sodium citrate solution as an anticoagulant. The blood was centrifugated for one hour at high speed, the plasma pipetted off as completely as possible, and the erythrocytes resuspended in the equivalent volume of a modified alkaline Locke's solution containing 7 Gm of sodium chloride, 2 Gm of sodium bicarbonate and 0.42 Gm of potassium chloride per liter of distilled water. In order to save time, the erythrocytes obtained at one bleeding were not used until the next, a donor's red blood cells being injected at the first bleeding. In view of the tendency to a decrease in the volume of red cells in these experiments, donor's erythrocytes were added as necessary to bring up the volume of the cells of the injected mixture to about the normal value of from 45 to 50 per cent. Occasionally reactions were observed suggesting incompatibility of bloods, but these were so rare as to warrant the omission of routine tests for iso-agglutinins. The dogs were usually bled twice daily, and ordinarily between 400 and 500 cc of blood would be withdrawn at each sitting. It was found advisable to begin reinjecting the warmed erythrocyte-saline suspension after the first bottle of blood had been drawn. The rest of the bleeding would be carried out while the suspension was running slowly into one of the veins of the leg. In this way serious shock was avoided, and the dogs were usually quite normal immediately after the procedure was completed. Puncture of the right side of the heart was safer than that of the left, because of the course of the coronary vessels. With a little preliminary training the animals could be bled without the use of any anesthetic or hypnotic drug. When bleeding from the external jugular veins was carried out, the dogs were kept sitting up and the head held high by an assistant, or else they were tied down on their backs while the head was allowed to project beyond the edge of the table and the snout strapped to an iron rod. An assistant compressed the vein just above the clavicle. No aseptic precautions were employed beyond ordinary cleanliness of glassware, needles and solutions. Usually 1,500 cc of 0.85 per cent sodium chloride solution was given daily in divided doses, by stomach tube. Edema fluid was obtained from the subcutaneous tissues by puncture of the skin with a large needle, care being taken to avoid drawing blood. Gentle squeezing of the surrounding tissues would yield enough fluid for analysis. Ascitic fluid was drawn off by syringe or suction through a large needle or at autopsy. Samples of blood were usually drawn from the external jugular veins and transferred to appropriate containers.

Chemical—The plasma proteins were estimated from the difference between the total nitrogen and the nonprotein nitrogen of the plasma, the following formula being used

$$[\text{Total nitrogen (grams per liter)} - \text{nonprotein nitrogen (grams per liter)}] \times 0.625 = \text{grams of plasma protein per hundred cubic centimeters}$$

The Koch-McMeekin²⁰ digestion method was used in the determination of the total plasma nitrogen. The distillation was carried out without transfer of the digestion mixture to another container. Tenth-normal acid and alkali were used in the titrations, with alizarin sulphonate as the indicator. The nonprotein nitrogen of the plasma was also determined according to Koch and McMeekin's method up to the end of the digestion process. The ammonia nitrogen was then distilled over into fiftieth-normal sulphuric acid and titrated with fiftieth-normal sodium hydroxide, phenol red being used as the indicator.

In the fractionation of the plasma proteins into albumins and globulins Howe's²¹ method was used for the precipitation of the globulins by means of

20 Koch, F. C., and McMeekin, T. L. *J. Am. Chem. Soc.* **46** 2066, 1924

21 Howe, P. E. *J. Biol. Chem.* **49** 109, 1921

22.2 per cent sodium sulphate. The entire procedure was carried out in a thermostat held at 37 C, and an interval of three hours elapsed between the precipitation and the filtration. The water-clear filtrate was analyzed for nitrogen by the method given for total plasma nitrogen. This value was subtracted from that of the total plasma nitrogen to give the globulin nitrogen. The albumin nitrogen was obtained by subtracting the nonprotein nitrogen from the filtrate nitrogen. The factor 0.625 was used to convert nitrogen values per liter into protein values per hundred cubic centimeters.

The serum calcium was estimated by the Clark-Collip²² modification of the Kramer-Tisdall method. The carbon dioxide content of the serum was obtained by means of the manometric procedure of Van Slyke and Neill²³. The cholesterol of the blood was determined by Leiboff's²⁴ method until April 25, 1929, and from then on by the following method. Extraction of 0.2 cc of blood by 12 cc of a 3:1 alcohol-ether mixture was carried out in the presence of kaolin. After thirty minutes, the mixture was centrifugated and the supernatant liquid decanted into a beaker, allowed to evaporate over night and the residue extracted with chloroform. The usual colorimetric procedure based on the color developed with acetic anhydride and sulphuric acid was then completed. The standard consisted of 0.4 mg of cholesterol in 10 cc of chloroform.

All of the chemical determinations were done in duplicate and blank analyses on reagents were frequently made.

Anatomic—Autopsies were performed by us on practically all of the dogs, and the various organs, with the exception of the central nervous system, were carefully examined. Histologic preparations were made from material fixed in a diluted solution of formaldehyde, U. S. P. (1:10). Unstained frozen sections of the kidneys and liver were studied with the polarizing microscope for the presence of doubly refracting lipoids (cholesterol esters). Great pains were taken to exclude confusing crystalline and amorphous precipitates, and in every instance the slide was warmed to bring out the characteristic fluid crystals. Without this precaution error is easy for the inexperienced investigator. Scarlet red was used as the stain for fat, with or without hematoxylin as a counter-stain. Paraffin or celloidin sections of various organs and tissues were prepared by standard methods and stained with hematoxylin and eosin. Blocks were cut from various portions of both kidneys, so that many sections were available for detailed scrutiny and a truly representative picture of the anatomic changes were obtainable.

RESULTS

In the preliminary report published in 1928¹⁶ and based on successful experiments on ten dogs, it was stated that "the edema usually begins when the plasma proteins have fallen to 3 per cent or less and recedes with a rise above that level if daily bleeding is discontinued." Observations are now available on more than forty dogs with varying degrees of edema. Table 1 shows the values for the plasma proteins in relation to the beginning and the decrease in gross edema. Unfortunately, it was not possible in all instances to estimate the plasma proteins for the day on which the changes in edema occurred. It is apparent,

²² Clark, E. P., and Collip, J. B. *J. Biol. Chem.* **63** 461, 1925.

²³ Van Slyke, D. D., and Neill, J. M. *J. Biol. Chem.* **61** 523, 1924.

²⁴ Leiboff, S. L. *J. Lab. & Clin. Med.* **10** 857, 1925.

however, that in general gross edema developed when the plasma proteins had fallen to about 3 per cent, and that definite decrease in edema usually occurred at a concentration of plasma protein between 3 and 4 per cent. Edema was never observed to begin when the plasma proteins were above 4.3 per cent and was never absent when they fell below 2.5 per cent, provided these respective levels for protein were maintained for twenty-four hours. Gross edema was chosen as the criterion in all these observations since it is something that can be seen, felt and weighed and does not require intricate calculations regarding the total water metabolism of the animal.

TABLE 1—*The Percentages of Plasma Protein During Increasing and Decreasing Edema*

Dog	Onset or Increase of Edema	Decrease in Edema	Dog	Onset or Increase of Edema	Decrease in Edema
4	3.01	4.74*	37	2.72	4.00
10	3.40	4.62*		3.33	
	3.82		38	3.58	4.25*
11	2.95		39	2.89	3.80
14	4.16		41	3.71	4.62
15	2.86			3.06	4.77*
16	2.71	3.57*	46	2.38	2.96*
17	2.89	2.64	47	3.70	4.14
	3.07	3.32	50	3.04	
	2.17	2.92	53	3.36	3.88*
	1.82	3.20*	54	2.80*	4.14*
20	2.32		55	3.24	
25	2.42	2.93	56	2.64	3.84*
26	2.84		57	2.57	3.05*
27	2.98			2.73	
28	4.31†		69	2.78†	3.64*
32	3.94		70	3.08†	3.46*
33	3.09	4.03		2.14	3.76*
34	3.76	4.20	71	2.38	3.74*
	2.83	5.34*	73	3.48†	
	3.54	3.90	86	2.48	4.53*
	3.63	4.16*		3.80†	3.66
	3.12	4.15		3.54	3.91*
35	2.42	4.17	89	2.78	5.14*
36	2.89	4.60*	90	2.04	3.44*
	2.28	3.00		2.57†	2.38*
	2.94	3.32		3.20	4.48*
	3.42	4.91*			
	3.39	3.94*			
	2.70				

* Twenty four hours or more after decrease in edema occurred

† Twenty four hours before edema appeared

The relation between plasmapheresis, concentration of plasma protein and edema is well illustrated in the protocols given in tables 1 to 4 and in figures 1 to 5. Whenever depletion of plasma is omitted for a single day, a prompt rise in the plasma proteins usually follows along with a definite decrease in the weight of the animal. This loss of weight is largely the expression of diuresis and disappearance of edema. The final weight reached may be considerably lower than the original control weight because of the decreased intake of food and the breakdown of tissue during the period of the experiments.

TABLE 2—*Protocols of Dogs in Which Edema Developed as a Result of Depletion of Plasma*

Dog	Date	Weight, Kg	Blood Drawn, Cc	Erythrocytes Returned, Cc *	Total Plasma Nitrogen, Gm per Liter	Plasma Nonprotein Nitrogen, Gm per Liter	Plasma Proteins, Gm per 100 Cc	Saline by Stomach Tube, Cc	Comment
4	3/26/28	10 0	870	810	9 44	0 38	5 66	1,500	This experiment was partly obscured by the mistaken use of pituitary extract subcutaneously
	3/27/28	10 8	895	895	4 48	0 30	2 61	1,000	
	3/28/28	11 2	920	895	4 48	0 83	2 28	1,500	
	3/29/28	11 6	920	920	4 81	0 49	2 70	1,500	Edema of walls of abdomen and chest
	3/30/28	11 8	460	460	5 11	0 30	3 01	1,000	
	3/31/28	11 2	460	460	5 45	0 33	3 20	1,800	Edema increasing
	4/ 1/28							600	Edema receding
	4/ 2/28	10 2	870	920	7 85	0 27	4 74	1,500	No edema
10	4/30/28	10 6	1,150	1,150	8 56	0 21	5 22	1,500	Some shock
	5/ 1/28	11 0	1,275	1,275	4 96	0 41	2 84	1,500	Moderate shock
	5/ 2/28	11 0	810	810	5 78	0 25	3 45	1,500	
	5/ 3/28	11 0	1,205	1,330				1,500	Edema of the legs, 25 cc of ascitic fluid aspirated
	5/ 4/28		410	460	5 85	0 40	3 40†	1,500	
	5/ 5/28	12 0	435	460	6 73	0 23	4 06	1,500	Edema more marked on abdominal wall
	5/ 6/28							500	Edema receding
	5/ 7/28	10 8	920	920	7 76	0 36	4 62	1,500	No subcutaneous edema, 60 cc of ascitic fluid aspirated
	5/ 8/28	10 6	920	920	6 93	0 22	3 82	1,500	Edema returning on lower part of abdomen, 225 cc of ascitic fluid drawn
	5/ 9/28	11 2	920	460	5 85	0 24	3 51	1,000	Increasing edema and ascites photographed, death from acute hemopericardium
11	5/10/28		335	335					Vomited about 400 cc of saline with food
	5/11/28	11 2	360	360	10 42	0 16	6 40	1,000	
	5/12/28	11 0	385	410	9 62	0 33	5 80	1,000	
	5/14/28	9 8	820	800	8 33	0 16	5 10	1,600	Chills
	5/15/28	10 6	920	1,000	6 73	0 22	4 07	1,500	
	5/16/28	11 2	920	1,000	5 13	0 41	2 95	1,500	Edema of external genitalia, but testis and perineum, 150 cc of ascitic fluid aspirated
	5/17/28	11 6	895	1,000	5 12	0 21	3 07	1,500	Edema spreading over walls of abdomen and chest, photographed
	5/18/28	12 8	895	1,000	4 08	0 41	2 29	1,400	Carbon dioxide content of serum, 24 02 millimols, increasing edema of the legs and parietes, much ascites
	5/19/28	13 2	435	500	3 52	0 25	2 04	1,500	Carbon dioxide content of serum, 19 9 millimols, serum calcium, 5 92 mg, enormous dependent edema considerable coughing
	5/20/28	14 0							Found dead, marked pulmonary edema, no pericardial effusion 1,500 cc of ascitic fluid, extreme anasarca

* In this and the following tables the figures in this column represent the theoretical volume of blood corresponding to the actual volume of packed erythrocytes, assuming a normal erythrocyte plasma ration of 1 1

† Blood sample taken after first dose of saline

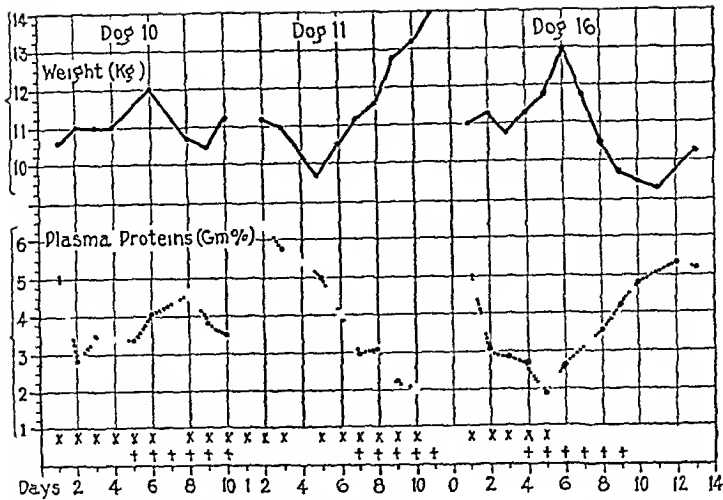


Fig 1—Showing the occurrence of edema and sharp gain in weight as the concentration of plasma proteins is reduced by acute plasmapheresis. The curve for dog 16 also illustrates the immediate decrease in weight due to diuresis, which occurs when the plasma proteins are allowed to increase above the critical level for edema.

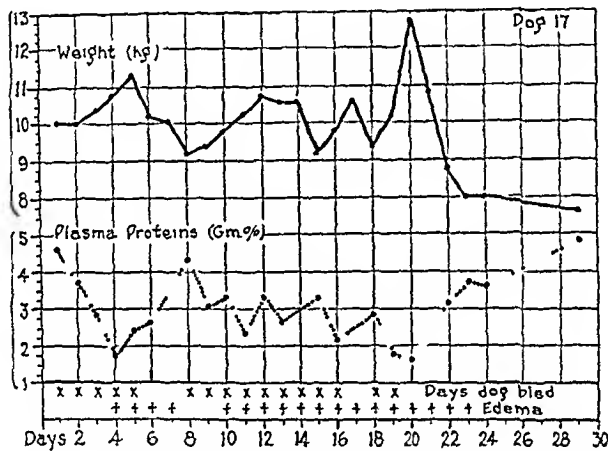


Fig 2—Periods of edema synchronous with levels of plasma proteins at or below 3 Gm per hundred cubic centimeters. In each interval between periods of plasmapheresis, the weight drops rapidly as the plasma proteins are restored.

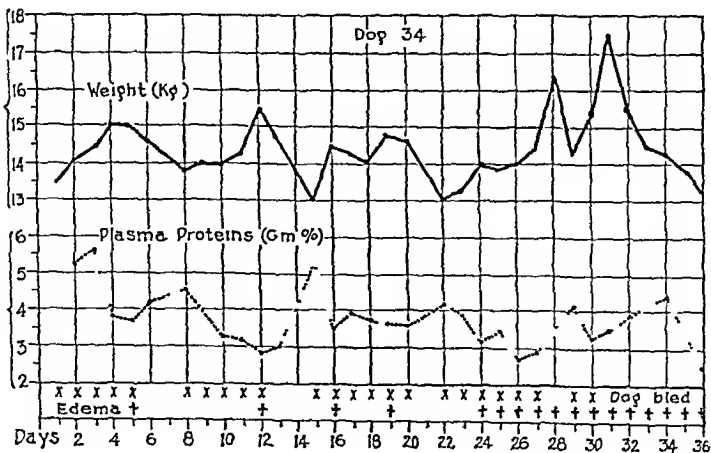


Fig 3—In this dog, the edema produced by plasmapheresis was exaggerated by the intravenous injection of Locke's solution administered on the day preceding each of the last two peaks in the weight curve.

The time of the first appearance of edema is interesting because it indicates the dependence of the transudates on the reduction of the plasma proteins. In most of the dogs used earlier, edema was first observed after from three to seven days of vigorous plasmapheresis.

TABLE 3—*Protocol of a Dog with Recurrent Periods of Edema During Plasmapheresis*

Dog	Date	Weight, Kg	Blood Drawn, Cc	Erythrocytes Returned, Cc	Total Plasma Nitrogen, Gm per Liter	Plasma Nonprotein Nitrogen, Gm per Liter	Plasma Proteins, Gm per 100 Cc	Serum Calcium, Mg per 100 Cc	Saline by Stomach Tube, Cc	Comment
17	6/18/28	10.0	845	825	7.54	0.14	4.63	10.53	1,000	
	6/19/28	10.0	770	800	6.25	0.28	3.74	8.94	1,500	500 cc of milk given
	6/20/28	10.4	770	800	4.72	0.10	2.89	7.86	1,500	Slight edema of prepubic region
	6/21/28	10.8	820	800	3.04	0.30	1.71	8.04	1,500	Carbon dioxide content of serum 24.6 millimols, not eating
										edema increasing over abdominal wall
	6/22/28	11.4	310	350	4.16	0.20	2.48	7.16	1,500	More edema, involving wall of chest
	6/23/28	10.2			4.48	0.27	2.64	8.78	1,500	Carbon dioxide content of serum 26.6 millimols, edema receding
	6/24/28	10.1								Slight edema
	6/25/28	9.2	885	850	8.00	1.02*	4.37*	9.40	1,500	No edema
	6/26/28	9.4	845	925	5.05	0.14	3.07	9.09	1,500	Chills, not eating, slight edema of lower part of abdomen
	6/27/28	9.8	845	725	5.78	0.37	3.38	9.23	1,500	Edema increasing, not eating
	6/28/28	10.2	820	700	4.01	0.16	2.41		1,500	More edema
	6/29/28	10.8	870	625	5.68	0.25	3.39	8.20	1,500	500 cc of milk given, considerable edema of thighs and abdomen, spreading to wall of chest
	6/30/28	10.6	895	600	4.64	0.32	2.67	8.37	1,500	Edema unchanged
	7/ 1/28	10.6	460	275					1,000	Swelling extended to neck, general condition good
	7/ 2/28	9.2	895	825	5.53	0.22	3.32	7.94	1,500	Much less edema
	7/ 3/28	9.8	845	700	3.68	0.19	2.17	7.12	1,500	Edema increasing rapidly again
	7/ 4/28	10.6							1,500	Marked diuresis and decrease in edema
	7/ 5/28	9.4	1,330	975	4.80	0.12	2.92	8.15	1,500	Edema increasing in the afternoon
	7/ 6/28	10.2	1,230	875	3.21	0.30	1.82	7.40		More edema
	7/ 7/28	12.8			2.96	0.30	1.66	6.30	1,600	Marked generalized edema and ascites, bilateral hydrothorax, photographed
	7/ 8/28	10.9							1,700	Marked diuresis, edema disappearing
	7/ 9/28	8.8			5.20	0.08	3.20	7.59		
	7/10/28	8.0			6.34	0.44	3.69	8.45		Trace of edema on the lower part of abdomen
	7/11/28	8.0			6.00	0.16	3.65	8.88		No edema
	7/16/28	7.6			8.00	0.26	4.84	9.08		

* Sample of blood drawn after first dose of saline. The value for nonprotein nitrogen is probably erroneous.

carried out without any intermission. On the other hand, in some of the later experiments relatively long periods of time elapsed before edema first appeared. This is to be explained partly on individual variations in the ability of the dog to regenerate plasma proteins and thus maintain them above the critical level, and partly on the fact that plasmapheresis was interrupted for periods of a day or two, during which considerable restoration of the plasma proteins could occur. Since there are more

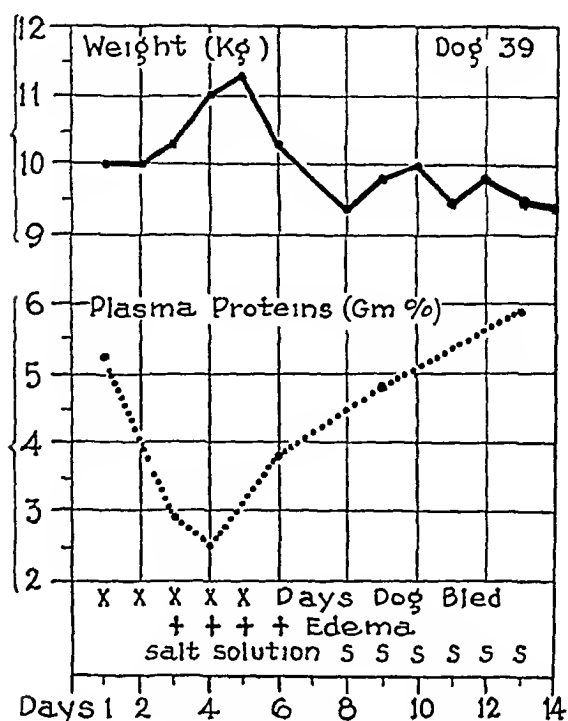


Fig 4—Typical edema in a dog bled from the external jugulars alone. Note the disappearance of edema after the sixth day, in spite of the continued administration of saline solution.

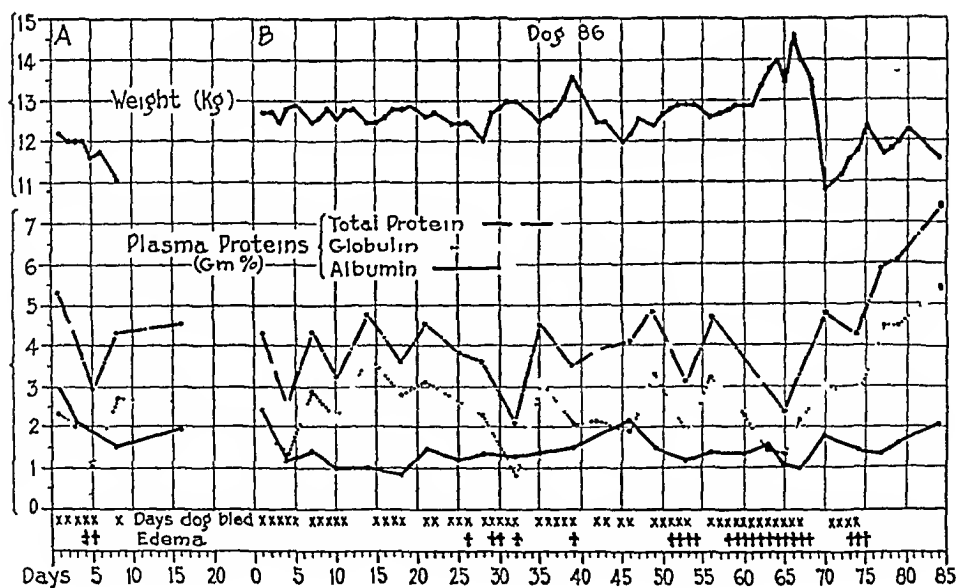


Fig 5—Chronic plasmapheresis is associated with periods of edema when the plasma proteins have been reduced to the edema level. In the intervals, however, edema rapidly disappears. The plasma globulin is more quickly restored than the plasma albumin.

plasma and more grams of plasma protein in a larger dog than in a smaller one, it will take considerably more bleeding to deplete the plasma and to bring on edema. If the quantity of plasmapheresis is inadequate, no edema will occur, even though daily bleeding is prac-

TABLE 4—*Protocol of Dog with Recurrent Edema as a Result of Plasmapheresis, Also Showing the Effects of Acute Hydræmic Plethora*

Dog	Date	Weight, kg	Blood Drawn, Cc	Erythrocytes Returned, Cc	Total Plasma Nitrogen, Gm per Liter	Plasma Nonprotein Nitrogen, Gm per Liter	Plasma Proteins, Gm per 100 Cc	Saline by Stomach Tube, Cc	Comment
34	10/29/28	13.5	460	250					No albuminuria
	10/30/28	14.1	920	895	8.63	0.08	5.35	1,000	Trace of albuminuria
	10/31/28	14.5	770	845				1,500	No albuminuria
	11/ 1/28	15.0	845	895	6.30	0.14	3.85	2,000	
	11/ 2/28	15.0	895	900	6.08	0.06	3.76*	2,000	Slight edema of thighs
	11/ 3/28	14.6			6.92	0.19	4.20		No edema
	11/ 5/28	13.8	920	875	7.48	0.18	4.56*	1,500	Heavy trace of albuminuria
	11/ 6/28	14.0	920	875				1,500	No albuminuria
	11/ 7/28	14.0	920	925	5.52	0.14	3.37*	1,500	No edema, good condition
	11/ 8/28	14.3	895	900	5.44	0.23	3.26	1,500	
	11/ 9/28	15.5	870	875	4.80	0.20	2.88	1,700	Slight edema of thighs
	11/10/28	14.7			5.08	0.25	3.02	1,000	Edema unchanged
	11/12/28	13.0	1,100	1,025	8.76	0.22	5.34	1,500	No edema
	11/13/28	14.5	1,025	950	5.87	0.20	3.54	1,500	Slight edema of thighs
	11/14/28	14.3	1,000	875	6.50	0.27	3.90	1,500	No edema
	11/15/28	14.1	920	900	6.44	0.34	3.81	2,000	No edema
	11/16/28	14.8	920	800	6.15	0.27	3.68	2,000	Slight edema of thighs
	11/17/28	14.7	1,050	1,050	5.94	0.17	3.61*	2,000	No change
	11/18/28								No edema
	11/19/28	13.1	895	900	6.85	0.20	4.16	1,500	Excellent condition, on bread and milk
	11/20/28	13.3	920	825	6.43	0.20	3.90	1,500	
	11/21/28	14.0	920	975	5.09	0.09	3.12*	1,500	Slight edema
	11/22/28	13.9	1,125	1,100	5.66	0.13	3.46*	1,500	No change, not eating
	11/23/28	14.0	1,150	1,100	4.60	0.20	2.75	1,500	Given meat, collapse after bleeding
	11/24/28	14.4	920	875	4.81	0.09	2.95*	1,500	Edema of thighs and buttocks, 2,175 cc of Locke's solution intravenously after last bleeding
	11/25/28	16.4							Rolls of edematous tissue along entire ventral aspect of body
	11/26/28	14.3	920	900	6.72	0.08	4.15	1,500	Still much edema
	11/27/28	15.4	820	825	5.38	0.08	3.32	1,000	Edema unchanged, 2,775 cc of Locke's solution intravenously, increasing edema
	11/28/28	17.5			5.80	0.23	3.48	1,500	Extreme edema, dyspnea, photographed
	11/29/28	15.5							Edema decreasing
	11/30/28	14.5			6.78	0.07	4.20	1,500	Not eating, less edema
	12/ 1/28	14.3			7.22	0.14	4.43		
	12/ 2/28	13.8							Dog quite weak, albuminuria
	12/ 3/28	13.3			4.53	0.44	2.56		Slight edema, death, 2 liters of bloody fluid in abdomen, spleen full of infarcts, marked pulmonary edema

* Sample of blood drawn after first dose of saline

ticed. If at any time, however, daily depletion of plasma is carried out to the proper extent in relation to the weight of the animal, edema will inevitably develop in less than a week. This may be clearly seen in the charts of our experiments and in the published protocols of Barker and Kirk.¹⁷

The distribution of the edema was quite constant in the different dogs. Pitting, soft edema was first observed along the inner aspect of the thighs, and about the external genitalia and the loose tissues of the lower part of the abdomen. Some ascites usually appeared at about the same time, or even earlier. As the edema increased more of the abdominal wall became swollen, and later the anterior and lateral thoracic walls. At the same time the perineal region and thighs increased in size and edema extended down the hind legs. The fore legs were rarely involved. The face was not affected. The subcutaneous fluid shifted readily with change in position of the animal. Figures 9 to 11 illustrate the edema observed in some of the dogs.

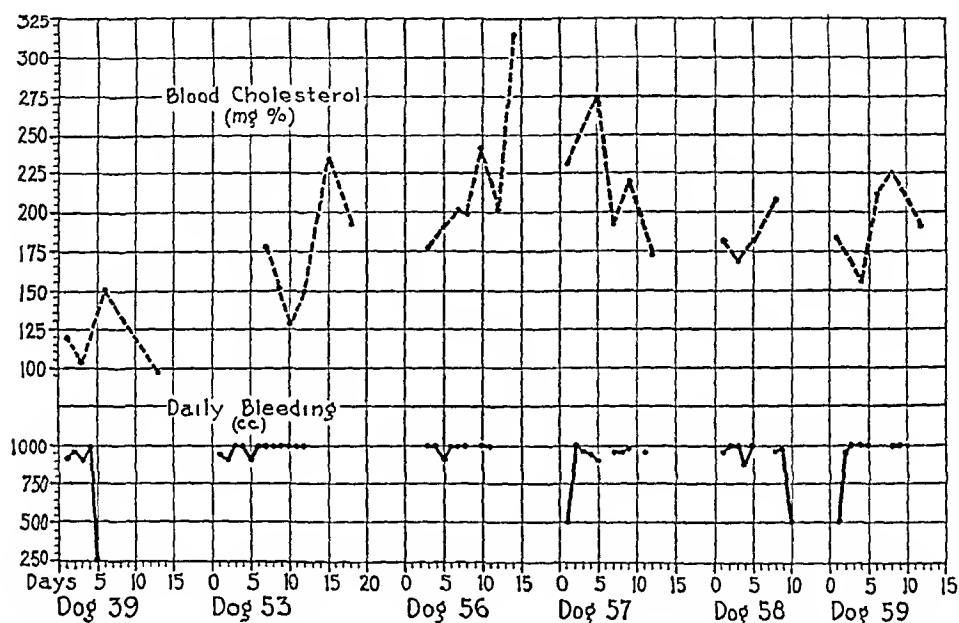


Fig 6—In acute plasmapheresis the blood cholesterol is quite variable, but it rises temporarily after the bleeding is discontinued

The edema fluid obtained by puncture of the skin is perfectly clear and limpid or shows a slight opalescence. With the heat and acetic acid test, only a faint trace of protein can be demonstrated. The ascitic fluid is usually opalescent, at times definitely lactescent. On centrifugation, some of the cloudiness may clear up. This fluid ordinarily gives a more definite qualitative test for protein than the subcutaneous transudate. Chloride and bicarbonate are found in the amounts expected for transudates. The chloride content of the edema fluid is always higher, by a few per cent, than the chloride concentration in the serum.

The most significant observation is the low protein content of these experimental transudates. The figures in table 5 show that, for the most part, the concentration of protein in the edema fluids is as low as that found in normal cerebrospinal fluid. The maximum protein

content of subcutaneous fluid is 0.25 per cent, of ascitic fluid, 0.47 per cent. Previous to the preliminary report of these analyses there had been no data in the literature on the protein content of experimental nephrotic transudates. The relation between our quantitative data and those available on other experimental edemas will be discussed later.

It was recognized early in this work that the myocardial damage resulting from repeated cardiac punctures might be an important factor in the edema produced. At least, it was something to be ruled out by bleeding the animals in another way. The external jugular veins were therefore utilized in a series of dogs. Typical edema appeared in the usual time, as shown in table 6 and figure 4. The transudates were not as extensive as in the previous cardiac group of dogs, but

TABLE 5—*The Low Protein Content in Experimental Nephrotic Edema in Dogs*

Dog	Edema Fluid	Protein, per Cent	Dog	Edema Fluid	Protein, per Cent
10	Ascitic	0.04	25	Subcutaneous	0.02
	Ascitic	0.12*		Ascitic	0.25
	Ascitic	0.06			
11	Ascitic	0.47	32	Ascitic	0.04
	Ascitic	0.24		Subcutaneous	0.01
	Subcutaneous	0.25	33	Ascitic	0.04
14	Ascitic	0.42	34	Ascitic	0.34
15	Ascitic	0.35		Subcutaneous	0.04
	Ascitic	0.02	37	Ascitic	0.02
	Subcutaneous	0.02			
16	Ascitic	0.39*	41	Ascitic	0.09
	Ascitic	0.11*		Ascitic	0.12
17	Subcutaneous	0.02*	56	Ascitic	0.01*
	Subcutaneous	0.05*		Ascitic	0.10*

* Only the total nitrogen was estimated on the edema fluid. The value for plasma non protein nitrogen was used in calculating the protein content.

this difference may be partially attributed to the difficulty in bleeding the animals for more than a few days, after which thrombosis of the veins set in. These experiments were reported briefly in 1929,²⁵ and have found further confirmation in the independent work of Barker and Kirk,¹⁷ who employed arterial bleeding as the method of obtaining depletion of plasma. It is an interesting fact that among the large number of dogs bled frequently from the heart not a single instance of chronic congestive heart failure has developed, in spite of severe myocardial trauma in some of the animals.

Another series of control experiments was planned to rule out the alkalinity of the modified Locke's solution used as the suspending medium for the erythrocytes. The high bicarbonate content of this solution was originally adopted in order to replace the bicarbonate lost in discarding the plasma. This solution was entirely unbuffered

and therefore unphysiologic. However, in a few dogs the p_H of the serum and the total carbon dioxide content were found to be normal at the height of edema. As an added control a solution²⁶ was made up containing sodium chloride, sodium bicarbonate, potassium chloride, disodium acid phosphate, potassium dihydrogen phosphate and calcium chloride in physiologic proportions and carbon dioxide passed into it to bring the p_H to 7.3. This solution was kept under paraffin oil. Difficulties were encountered during its use owing to the tendency of the erythrocyte suspension to coagulate in some instances. However, several experiments were carried through to the stage of edema. This developed in the typical location and had the usual low protein content.

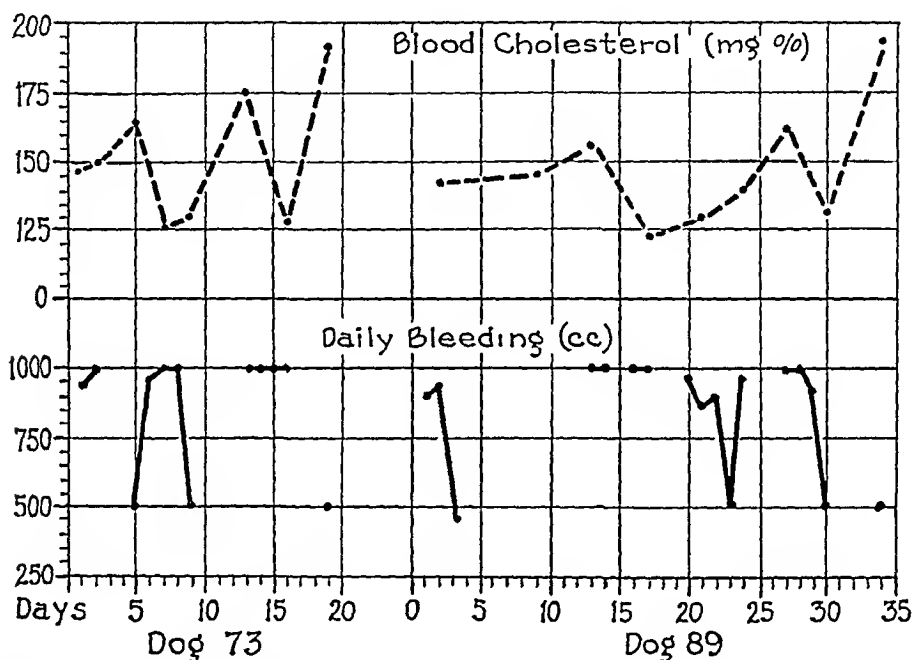


Fig 7—In longer experiments the blood cholesterol shows a cyclic fluctuation, the peaks occurring in the intervals between periods of plasmapheresis

The rôle of starvation, or at least of undernutrition, presented itself next as a factor to be controlled. Although most of the dogs ate heartily throughout the course of the experiments, it could not be denied that the bleedings, twice a day, might deprive the animal of most of the absorbed elements of food. In a number of instances the blood was definitely lipemic, suggesting that the plasmapheresis had coincided with the absorptive alimentary lipemia. This occurred in spite of the fact that the dogs were usually fed late in the afternoon after the day's plasmapheresis was over. Dogs were therefore starved for a week or more, but were given 0.85 per cent saline by stomach

²⁶ Prof. A. B. Hastings furnished us with the composition and the method of preparation and storage of this solution.

TABLE 6—*Protocols on Dogs Bled from the External Jugular Veins Instead of From the Heart*

Dog	Date	Weight, Kg	Blood Drawn, Cc	Erythrocytes Returned, Cc	Total Plasma Nitrogen, Gm per Liter	Plasma Nonprotein Nitrogen, Gm per Liter	Plasma Proteins, Gm per 100 Cc	Saline by Stomach Tube, Cc	Comment
39	3/25/29	10 0	845	975	8 54	0 24	5 19	1,500	Blood cholesterol, 118 mg per 100 cc, blood drawn from external jugulars
	3/26/29	10 0	895	1,050				1,500	
	3/27/29	10 3	845	975	4 76	0 14	2 89	1,500	Edema of external genitalia and thighs
	3/28/29	11 0	920	950	4 20	0 16	2 53*	1,500	Edema spreading over walls of the abdomen and chest
	3/29/29	11 3	230	250				1,500	Edema increasing, jugulars closed, photographed
	3/30/29	10 3			6 30	0 22	3 80		Much less edema, blood cholesterol, 152 mg
	4/ 1/29	9 4						1,500	No edema
	4/ 2/29	9 8			7 91	0 21	4 81*	1,500	1,500 cc of saline daily from 4/2 to 4/6
	4/ 6/29	9 6			9 73	0 26	5 92*	1,500	No edema since 4/1, blood cholesterol, 97 mg
46	3/11/29	10 8							Blood drawn from external jugulars
	3/12/29		460	475				500	
	3/13/29	10 8	920	925	7 00	0 20	4 25	1,500	
	3/14/29	10 6	920	1,050				1,500	
	3/15/29	10 0	895	1,000	3 78	0 24	2 22	1,500	Jugulars closing, no edema
	3/16/29	10 3	410	475	4 06	0 26	2 38	1,500	Edema of thighs and external genitalia, 40 cc of aseptic fluid aspirated
	3/17/29	10 6							Edema persisted unchanged
	3/18/29	10 6						1,500	Decrease in edema
	3/19/29	10 3			4 88	0 14	2 96	1,500	Slight edema
	3/20/29	10 3						1,500	No edema, saline continued daily
	3/29/29	10 4			7 63	0 19	4 68*	1,500	No edema since 3/20
47	3/18/29	12 0	845	1,000	10 50	0 16	6 46	1,500	Blood drawn from external jugulars
	3/19/29	12 4	820	925				1,500	500 cc of milk given
	3/20/29	12 6	870	975	6 10	0 17	3 70*	1,500	Edema of external genitalia
	3/21/29	13 2	795	925	5 40	0 24	3 23	1,500	Edema increasing rapidly, cough
	3/22/29	13 2	230	250				2,500	Jugulars closed, edema unchanged
	3/23/29	12 8			6 71	0 09	4 14*	1,500	Less edema
	3/25/29	12 0						1,500	No edema
	3/26/29	12 0			7 56	0 16	4 63	1,500	No edema, good condition

* Sample of blood drawn after first dose of saline

TABLE 7—*The Plasma Proteins During Starvation*

Dog	Days of Starvation	Initial Weight, Kg	Final Weight, Kg	Initial Plasma Proteins, Gm per 100 Cc	Final Plasma Proteins, Gm per 100 Cc	Total Saline Given by Stomach Tube, Cc
38	6	11 0	10 3	5 53	5 57	7,000
39	11	10 0	9 1	5 76	5 88	10,000
43	7	8 2	7 8	6 23	6 90	8,500
46	12	10 4	9 7	4 68	3 97	12,500
47	8	12 8	12 0	5 49	5 40	10,500
48*	7	9 2	8 0	4 64	4 63	9,000
49	7	9 3	9 1	4 96	4 67	8,500

* This dog died of bronchopneumonia on the last day

tube The plasma proteins were essentially unaffected by starvation, as had been shown years ago by Kerr, Hurwitz and Whipple²⁷ No gross edema developed Loss of weight occurred in the seven dogs, varying between 2 and 9 per cent of the initial body weight Table 7 gives a summary of these experiments

The daily administration of 1,500 cc of 0.85 per cent sodium chloride solution to a dog of 10 Kg may seem to be a rather excessive dose However, dogs can dispose of even larger amounts of salt and water without developing edema As a matter of fact, one of the probable reasons why McIntosh and Leiter²⁸ were unable to produce edema by acute plasmapheresis in more than two dogs of a considerable number was the daily administration to these dogs of about 40 Gm of sodium chloride as a hypertonic solution This resulted in a negative chloride balance even in dogs in which diarrhea did not develop Rela-

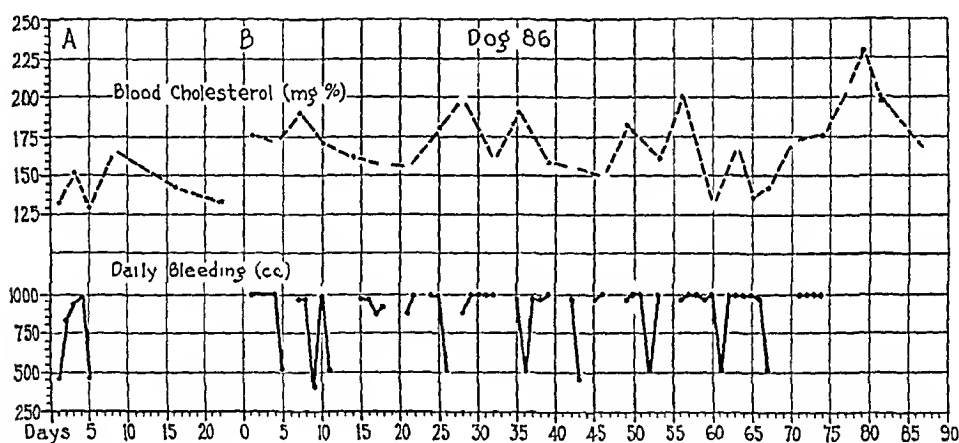


Fig 8—In spite of repeated increases in the blood cholesterol, there is no tendency for a persistent hypercholesterolemia in this chronic experiment

tive to body weight, the dog's kidneys have a remarkable capacity to dispose of chlorides In the present experiments, as shown in figure 4, the continued administration of saline has little or no influence on the tide of disappearing edema once the plasma proteins have surpassed the critical edema level At most, a slight hump in the weight curve manifests itself for a day or two

In nephrotic Bright's disease a low concentration of plasma protein is usually associated with a low albumin-globulin ratio This has often been attributed to the fact that most of the protein lost in the urine is plasma albumin, but little of it is plasma globulin In experimental

27 Kerr, H J , Hurwitz, J H , and Whipple, G H Am J Physiol **47** 356, 1918

28 McIntosh and Leiter Unpublished observations of experiments during 1925 and 1926



Fig 9 (dog 10) —Ascites and edema of the abdominal wall, perineum and thighs (See table 2 and fig 1)



Fig 10 (dog 17) —Ascites and edema of the wall of the lower part of the abdomen, external genitalia and hind limbs (See table 3 and figs 4 and 5)

TABLE 8—*Protocol of Long Experiment Showing the Effects of Depletion of Plasma on the Plasma Albumin and Globulin and the Blood Cholesterol—Continued*

Dog	Date	Weight, Kg	Blood Drawn, Cc	Erythrocytes Returned, Cc	Plasma Nonprotein Nitrogen, Gm per Liter	Plasma Proteins, Gm per 100 Cc	Plasma Albumin, Gm per 100 Cc	Plasma Globulin, Gm per 100 Cc	Blood Cholesterol, Mg per 100 Cc	Saline by Stomach Tube, Cc	Comment
B	3/10/30	12.5	895	1,000	0.13	4.83	1.51	3.32	183	1,500	
	3/11/30	12.7	920	1,000						1,500	
	3/12/30	12.8	920	950						1,500	Slight edema of thighs
	3/13/30	12.9	460	500						1,500	
	3/14/30	12.9	920	1,000	0.22	3.09	1.18	1.91	161	1,500	
	3/15/30	12.9								1,000	
	3/17/30	12.6	895	925	0.26	4.66	1.38	3.28	200	1,500	Convulsion, no edema
	3/18/30	12.7	920	1,000						1,500	
	3/19/30	12.8	920	1,000						1,500	Slight edema
	3/20/30	12.9	895	975						1,500	More edema
	3/21/30	12.9	920	1,000	0.16	3.62	1.33	2.29	130	1,500	
	3/22/30	12.9	460	275						1,500	Edema increasing
	3/23/30	13.4	920	825						1,500	
	3/24/30	13.8	920	1,000	0.13	2.97	1.51	1.46	171	1,500	
	2/25/30	14.0	920	1,000						1,500	Marked edema of external genitalia, legs, etc
	3/26/30	13.5	920	1,000	0.15	2.42*	1.06	1.36	134	1,500	
	3/27/30	14.6	895	825						2,500	Ascites, edema of walls of abdomen and chest, hemolytic icterus
	3/28/30	14.0	460	425	0.20	3.23	1.02	2.21	142		Edema unchanged, icterus decreasing
	3/29/30	13.5								1,000	Edema decreasing rapidly
	3/31/30	10.8			0.19	4.79	1.80	2.99	172		No edema, good condition
	4/ 1/30	11.0	920	950						1,500	Double rations from this date
	4/ 2/30	11.2	920	1,000						1,500	
	4/ 3/30	11.6	920	1,000						1,500	Edema of thighs
	4/ 4/30	11.8	920	1,000	0.16	4.28	1.49	2.79	175	1,500	
	4/ 5/30	12.6								1,000	Edema more marked
	4/ 7/30	11.7			0.21	5.93	1.41	4.52	206	1,500	No edema
	4/ 8/30	11.8									
	4/ 9/30	12.0			0.15	6.13	1.61	4.52	230	1,500	Acute arthritis of both ankles
	4/10/30	12.3								1,000	
	4/11/30	12.4			0.11	5.33	1.91	3.42	195		
	4/12/30	12.4									
	4/14/30	11.6			0.34	7.56	2.03	5.53	216		Condition good
	4/15/30	11.8									Ankles normal
	4/16/30	12.0									
	4/17/30	12.2			0.16	7.24	1.71	5.53	165		
	4/18/30	12.4									Eating well
	4/19/30	12.5									Sudden dyspnea and death from acute pulmonary edema, no ascites

* Sample of blood drawn after first dose of saline

the immediate increase in the plasma proteins, subsequent to discontinuance of plasmapheresis, is largely due to a rise in the globulin fraction²⁹. The parallelism between the total protein and the globulin curves is often striking. In the experiments of two weeks' duration or less no such regularity is ordinarily evident. It takes considerable time for plasma albumin to regenerate, although there is much variation

in individual dogs. The edema level of the concentration of plasma protein is determined not simply by the amount of plasma albumin, but by the resultant of the colloidal osmotic pressure due to both the albumin and the globulin fractions. Increase in globulin, if sufficiently developed, may counteract the effects of a low or even decreasing plasma albumin.

The rapid restoration of plasma globulin is not entirely dependent on a good state of nutrition of the animal. In dog 90, for example, the emaciation manifested by a fall in body weight from 12.6 to 8.9 Kg. in the course of thirty days was not sufficient to prevent the typical sharp rise in the plasma globulin curve at the end of this experimental period. No dog was observed in which a significant increase in plasma



Fig. 11 (dog 34) — Dog with massive rolls of edematous anterior thoracic and abdominal walls, following acute hydremic plethora during a period of hypoproteinemia. (See table 4 and fig. 6.)

globulin did not occur within from twenty-four to forty-eight hours after bleeding was interrupted.

When cholesterol of the blood was used as an indicator for the blood lipoids, a curious series of results was obtained.²⁹ In the short experiments (fig. 6) no consistent trends could be made out. However, with prolonged depletion of plasma there appeared a more or less definite cycle of hypocholesterolemia during active bleeding followed by temporary hypercholesterolemia in the intervals free from plasmapheresis. Similar conditions are evident in some of the protocols of Barker and Kirk,¹⁷ although these authors have drawn rather different conclusions from their results. Figures 7 and 8 and table 8 indicate the cycles described. While it is possible that the lower values for

blood cholesterol during vigorous production of depletion of plasma may depend partly on a decreased concentration of erythrocytes, this is not probable in view of the fact that the reinjected erythrocyte-saline mixture was practically always made up to a normal relative volume of red corpuscles by the addition of donor's erythrocytes. However, this phase of the problem will bear repetition, plasma cholesterol instead of the whole blood cholesterol being used as the basis for comparison.

The anatomic changes observed during these experiments were of considerable variety. Some were due directly to the procedure employed, others were incidental. The changes in the heart and kidneys were the most significant. Such lesions as bronchopneumonia, infarcts or



Fig 12—Typical subcutaneous and intermuscular edema in dog 32. Low power view.

abscesses in the lungs and spleen of some animals and traumatic hemothorax require no comment. If the dog died during a period of active edema, ascites, pleural effusions and pulmonary edema were common accompaniments of subcutaneous anasarca. Occasionally hemolytic icterus developed from the rapid destruction of foreign blood.

In the heart, a great many traumatic lesions were encountered. These were largely the result of the needle punctures. There were linear areas of hemorrhage, necrosis, leukocytic infiltration and various stages of repair by granulation in the myocardium of the right and left ventricles and often in the septum. In spite of a great number of puncture wounds, the pericardial sac was never completely obliterated, nor was there any gross suppuration except in two dogs, one of which

(dog 25) had a severe infection of the respiratory tract. Usually the parietal pericardium was thickened and adherent over the anterior aspect of the right ventricle, in which most of the punctures were made. Localized deposits of fibrin were also seen. The endocardium was frequently lacerated, and mural thrombi were common. In a number of dogs considerable damage was done to the tricuspid, aortic and mitral valves, with resulting vegetations of a friable character that gave rise to emboli. Fibrous thickenings and fusion of valves were seen in some dogs, involving particularly the tricuspid and mitral valves. Puncture of a coronary vein or artery on the surface of the heart invariably led to death within a matter of minutes and could be diagnosed from the clinical symptoms after a few experiences. Only occasionally was a mass of fibrin found in the pericardium, indicating a previous nonfatal hemopericardium. Dogs 17, 34, 86 and 89, which had periods varying between fifteen and fifty-four days of actual bleeding, involving a minimum of from 52 to 198 cardiac punctures, showed no gross blood or residual coagulum in the pericardial sac at autopsy.

The kidneys were the seat of several types of pathologic processes. In the first place, gross infarcts were common because of the frequency of endocardial thrombosis. These infarcts were bland or frankly infected. In dogs 71, 73, 86, 89 and 90, in which time for organization of the infarcts was available, there was extensive calcification of necrotic tubules and glomeruli, along with the usual interstitial fibrosis and some round cell infiltration. In these areas, also, exquisite masses of doubly refractile lipid droplets could be seen in the casts and atrophying tubular epithelium. Another lesion was localized cortical suppuration, in the form of acute glomerulitis and periglomerulitis, of embolic origin, often associated with linear leukocytic infiltration and necrosis extending to the lower cortex or ending in abscesses in various levels of the medulla. These changes in the kidney, like the infarcts, were easy to understand. Another type of process, however, gave more trouble. This consisted of multiple irregular or linear foci of large mononuclear cells ("plasma cells") with a smaller number of lymphocytes and polymorphonuclears, found about the interlobular arteries and veins or around the glomeruli and between the tubules, often extending through the entire cortex and obviously leading to compression atrophy of the tubules coursing through these cellular masses. In some kidneys the infiltrates were near an infarcted or suppurative area. In others, however, they constituted the only lesions. There were clearcut transitions between such mononuclear, perivascular infiltrates in the cortex and definite linear or wedge-shaped scars in which tubules had atrophied or disappeared while glomeruli were still preserved but with concentric

layers of fibrous connective tissue about the capsules and some shrinkage of the entire tuft. The vessels in these scarred areas were not significantly altered. Such scars, when numerous, may give the superficial impression of a contracted kidney because of the pits and depressions on the surface. A large amount of normal parenchyma, however, is usually present between the narrow scars. It is in this group of renal lesions, probably, that one must place the changes described by Barker and Kirk¹⁷ and Barker,³⁰ who attributed them directly to a humoral effect of the altered blood plasma and speculated on their possible relation to human contracted kidneys. These lesions will be discussed in more detail later on.

Fatty changes in the form of irregular accumulation of large droplets in cells of ascending limbs of Henle's loops and the terminal straight portions of the proximal convoluted tubules in the lower part of the cortex were observed rather frequently. Practically none of this fat was doubly refractile. Fatty casts and calcified casts or epithelium in various levels of the medulla were inconstant observations. Careful search for doubly refractile lipid droplets revealed a few typical fluid crystals in many of the convoluted tubules in the middle of the cortex. These droplets were usually seen at the apex of the cells or actually in the narrow lumen. Like the ordinary fat in the inner cortex, these isolated droplets probably represent a physiologic condition. No changes were observed in the convoluted tubules comparable to the typical morphology of chronic nephrosis in man.

COMMENT

The low protein content of the edema fluid produced by depletion of plasma establishes it as a nephrotic type of edema analogous to the transudates in nephrotic Bright's disease, in war edema and in other nutritional dropsies. The correlation between low serum or plasma proteins and the presence of nephrotic edema in man is so well established³¹ that it requires no further review here. In rats a nutritional edema, probably nephrotic, has been repeatedly produced by diets low in protein only³² and correlated with reduction in serum proteins.³³ Harden and Zilva³⁴ commented on a nutritional edema observed in a monkey. Through the cooperation of Dr I. S. Falk, formerly in the Department of Bacteriology of the University of Chicago, the data

30 Barker (footnote 18, first reference)

31 Leiter, L. Nephrosis, *Medicine* **10** 135 (May) 1931

32 Kohman, E. A. *Am J Physiol* **51** 185 and 378, 1920. Frisch, R. A., Mendel, L. B., and Peters, J. P. *J Biol Chem* **84** 167, 1929

33 Frisch, Mendel and Peters (footnote 32, second reference)

34 Harden, A., and Zilva, S. S. *Lancet* **2** 780, 1919

shown in table 9 have been obtained and represent the first published analyses on a nephrotic type of edema in the monkey. The exact origin of the nutritional disturbance is unknown. Histologic examination of the kidneys eight weeks after the original edema had subsided revealed no pathologic changes. Figure 13 shows the edema of the eyelids in this monkey.

The edema produced in dogs has been shown to be definitely related to a decrease in the plasma proteins to approximately half of the normal



Fig 13—Edema of the eyelids in a monkey that also had edema of the abdominal wall and perineum (See table 9)

value. A slight increase in the plasma proteins above this level has been regularly associated with decrease or disappearance of edema. The rapidity with which this change occurs speaks strongly in favor of a simple disturbance in the equilibrium of mechanical forces determining the interchange of fluids between the capillaries and the tissue spaces. No nutritional disturbance of the walls of the capillaries, as might be postulated to be the consequence of the hydremia, no cardiac or renal insufficiency and no change in the tissue colloids can reasonably be assumed to afford a better explanation of this rapid change in water balance. Furthermore, since the capillaries are normally freely permeable to salt and water in both directions,³⁵ any theory involving

³⁵ Krogh, August. *Anatomie und Physiologie der Capillaren*, Berlin, Julius Springer, 1924.

altered permeability to salt and water as a result of some toxic or functional change in the wall of the capillary has little significance. If, on the other hand, the true concept of permeability of the capillaries is understood, that is, the permeability to the plasma proteins, there is no evidence that the experimental edema described is related to increased permeability. There is almost no protein in the edema fluid. This observation is in striking contrast to practically all of the experimental edemas previously reported. Thus, the ascitic fluid in uranium

TABLE 9—*Protocol on a Monkey with Nephrotic Edema of "Spontaneous" Development*

Date	Weight, kg	Total Plasma Nitrogen, Gm per Liter	Plasma Nonprotein Nitrogen, Gm per Liter	Plasma Proteins, Gm per 100 Cc	Protein in Edema Fluid, Gm per 100 Cc	Comment
1/12/29		5.90	0.53	3.36*		Edema of the abdominal wall, perineum and thighs, diarrhea
1/16/29	3.475					Edema unchanged, blood creatinine, 1.16 mg
1/17/29	3.350					Blood urea nitrogen, 14.3 mg, trace of albumin in the urine
1/19/29	3.475					Edema of the scalp, eyelids and cheeks, eating ravenously
1/21/29	3.375	6.29	0.20	3.80		No edema of the face, persistent edema of the perineum and lower part of abdomen
1/23/29	3.400				0.39	About 10 per cent blood in this sample of edema fluid
1/24/29	3.375	5.38	0.21	3.23	0.12†	Edema decreasing
1/25/29	3.150					Morning edema of the face, photographed
1/29/29	3.150					No diarrhea, edema decreasing
2/ 4/29	3.000					Slight edema of abdominal wall
2/ 9/29	2.900					No edema
2/11/29	2.800					No edema, good condition
2/19/29	2.900	7.56	0.39	4.48		Returned to Dr. Falk's laboratory
2/23/29	2.900					Died in emaciated state with moderate peripheral edema and some ascites, no tuberculosis, no nephritis
4/11/29		4.69	0.46	2.66		

* The percentage of plasma protein in two normal monkeys was 6.28 and 6.84.

† The protein content of ascitic fluid from a monkey with tuberculous peritonitis was 2.85 per cent. The percentage of plasma protein was 4.93.

edema coagulates spontaneously and has a protein content ranging between 1 and 3 per cent³⁶. This indicates a close relationship to the inflammatory edemas produced by such obvious vascular poisons as mustard oil, paraphenylenediamine and dionin, in which the exudate is often whole plasma³⁷. Similarly, the edema recently produced by subcutaneous administration of Ringer's solution to bilaterally nephrec-

³⁶ Garnier, M., Schulmann, E., and Marek, J. *Compt rend Soc de biol* **99** 269, 1928. Nau, A. *Compt rend Soc de biol* **99** 869, 1928. Govaerts, P. *Bull Acad roy de med de Belgique* **9** 33, 1928. Georgopoulos (footnote 8).

³⁷ Tainter, M. L., and Hanzlik, P. *J Pharmacol & Exper Therap* **24** 179, 1924.

tomized dogs also has a protein content between 1 and 3 per cent³⁸ It is fair, therefore, to state that none of these experimental edemas is pathogenetically related to nephrotic edema. Conversely, clinical and experimental nephrotic edemas are primarily not problems of permeability of the capillaries, but rather disturbances in the normal equilibrium between hydrostatic and protein osmotic forces. The experimental nephrotic edema in dogs thus represents the first direct evidence in favor of the Starling-Epstein-Krogh theory of filtration edemas. In dogs, the edema is uncomplicated by factors of permeability. In man, especially in early nephrotic glomerulonephritis, the capillaries may remain partially injured shortly after the acute stage of the disease, so that edema fluid obtained during this period may contain protein intermediate in value between nephrotic and acute nephritic edemas. On the other hand, in hunger edema there is no evidence of increased permeability of the capillaries to protein.

The edema in dogs differs from the purely nutritional edemas of man and experimental animals in being a much more acute process. While in the rat it takes about two months of feeding on a low protein diet before edema manifests itself, plasmapheresis in the dog is only a matter of days. The period of undernutrition requisite to produce edema in man is still an unknown quantity. On the other hand, the direct loss of plasma proteins in the dog is a more violent disturbance than the gradual depression of the building of plasma proteins because of the inadequate supply of their elements in undernutrition. The intensity of the process in the dog, therefore, more than outweighs the time factor in ordinary nutritional edemas. A clinical parallel is seen in those cases of acute glomerulonephritis in which a marked albuminuria persists from the start, so that within a relatively short time the plasma proteins become reduced to the level of the edema. It is perhaps reasonable to assume that in all these clinical and experimental states one is dealing with different degrees of the same underlying process.

The rôle of salt and water in the edema of dogs would seem to be relatively simple. The administered saline is not the cause of edema any more than salt and water are the actual cause of most clinical edemas. However, no edema is possible without an endogenous or exogenous supply of the chief constituents of edema fluid. Hence, all intercellular edemas are to this degree dependent on a proper supply of salt and water. Therefore, it is not at all remarkable that patients may lose some of their edema without any significant increase in the plasma proteins, provided they are kept on a low intake of salt and

38 Farmer, C. J., Barry, F. S., Reed, A., and Ivy, A. C. *Proc. Inst. Med.*, Chicago, 1930, vol. 8.

fluid or are given diuretics that somehow produce a negative salt and water balance. Govaerts³⁹ made this point clear. This situation has been repeatedly overlooked by authors who are unwilling to accept the important position of the plasma proteins in certain clinical edemas. In the dog, the same amount of salt and water that produced edema when the level of plasma protein was below 3 per cent fails to have any effect when the plasma proteins reach 3.5 or 4 per cent. Although the actual experiment has not been carried out, there is little doubt but that it should be possible to keep a dog entirely free from edema on a rigidly salt-poor and low fluid diet even with the plasma proteins reduced to the level for edema. In patients or animals with the plasma proteins just at the critical level, the effect of the intake of sodium chloride and water on the presence of edema will naturally be more striking because under these conditions the body responds quickly one way or the other. This is well illustrated in cachectic states, in hunger edema and in various other nutritional edemas in which the plasma proteins may be only moderately reduced. Rest in bed and restriction of salt and fluid are often excellent diuretics in such patients.

The rapidity with which the dog can regenerate plasma proteins even during emaciation is a surprising phenomenon, but again illustrates the large factor of safety involved in all vegetative functions. How much the ordinary fractionation of the plasma proteins really means concerning the actual nature of the proteins involved is unknown, yet the results have been quite consistent in indicating a more rapid formation of the globulin fraction than of the albumin fraction. It must be admitted, however, that the effect of infection was not controlled in our dogs. It is interesting at this point to consider the work of Bruckman, D'Esopo and Peters,⁴⁰ who observed that the serum albumin was essentially the only fraction reduced in the moderate hypoproteinemia of malnutrition from various causes. Improved nutrition was associated with an increase in the serum albumin. Edema occurred in the patients with low serum proteins and could be fairly well correlated with low serum albumin.⁴¹ The absolute quantity of plasma proteins lost daily by dogs undergoing plasmapheresis has not been determined, but it is safe to estimate that it corresponds to a severe albuminuria in man. Both the patient with nephrotic Bright's disease and the dog may maintain a fairly constant level of plasma proteins while losing 10 Gm or more of protein a day. They are both regenerating proteins.

39 Govaerts, P., and Cordier, R. *Bull Acad roy de med de Belgique* 8: 510, 1928.

40 Bruckman, F. S., D'Esopo, L. M., and Peters, J. P. *J Clin Investigation* 8: 577, 1930.

41 Bruckman, F. S., and Peters, J. P. *J Clin Investigation* 8: 591, 1930.

quite actively. One wonders, therefore, what the patient could do if he were really able to procure and assimilate large amounts of food protein. Although the high protein therapy of nephrotic Bright's disease has been suggested and championed by Epstein⁴² for many years, no systematically controlled study of the effects of varying amounts of dietary protein in this disease has been available until the recent work of Peters and Bulger⁴³ and of Berglund and his associates⁴⁴.

In recent years there has been a considerable tendency to ascribe practically all of the demonstrable biochemical and morphologic changes in the nephrotic syndrome to the loss of plasma protein in the urine. It does not matter for this point of view whether the protein is or is not biologically foreign to the organism. The important fact is its escape from the plasma. The relatively constant hypercholesterolemia (lipoidemia) in the active stages of the nephrotic syndrome naturally suggested a systematic study of the cholesterol of the blood in the dogs undergoing plasmapheresis. Baiker and Kirk¹⁷ reported increases in blood cholesterol up to 254 mg per hundred cubic centimeters, and correlated this with the well established data on patients with nephrosis. An examination of their published protocols actually leads to the conclusion that active depletion of plasma results in a definite hypocholesterolemia with a temporary rebound to higher values when bleeding has been interrupted. Our results, obtained on a more representative series of dogs, also seem to indicate that plasmapheresis and edema are associated with a decrease in the blood cholesterol. This is a picture exactly the opposite of the situation in the nephrotic syndrome in man. In the latter, the blood cholesterol usually remains elevated for long periods during the albuminuric, edematous stages of the disease, falling toward normal when the cardinal symptoms clear up. Granting this difference between the experimental nephrotic edema and the clinical nephrotic syndrome, it is obviously incorrect to describe the experimental condition as "nephrosis" and to attempt to force it into more or less complete alignment with nephrotic Bright's disease, as Baiker and Kirk¹⁷ have done. Why it is that nephrotic Bright's disease is characterized by an increase in blood cholesterol while hunger edema, with essentially the same type of transudates, usually is associated with a decrease in blood cholesterol, remains a difficult puzzle. The gaps in the knowledge of lipid metabolism are too many to allow anything but a guess as to the reasons for the curves for blood cholesterol observed in dogs.

42 Epstein, A. A. *Arch f Verdauungskr* **44** 31, 1928, footnote 14.

43 Peters, J. P., and Bulger, H. A. Relation of Albuminuria to Protein Requirement in Nephritis, *Arch Int Med* **37** 153 (Feb) 1926.

44 Berglund, H. Symposium on the Kidney, Minneapolis, July, 1930.

One may conclude from the foregoing discussion that experimental nephrotic edema is far from being synonymous with the nephrotic syndrome in man. A symptom, edema, has been produced, and not much else. There still remains to be considered the so-called renal lesion of plasmapheresis. Barker³⁰ stated that "a secondary contracted kidney may well follow a long standing low proteinemia as a result of tubular atrophy and scar tissue replacement" (page 609). Earlier, Barker and Kirk¹⁷ were not quite so definite in their conclusions, although they wrote that "the experimental results tend to support the theory that the continual loss of albumin in the urine is sufficient alone to produce renal pathologic changes" (page 345). If this point of view could be established beyond a reasonable doubt, it would represent an important contribution toward the explanation of the contracted kidneys the etiology of which is not an obvious chronic glomerulonephritis or arteriolar sclerosis. As a matter of fact such kidneys, excluding, of course, hydronephrotic and pyelonephritic types, are extremely rare. Furthermore, there are so few cases of proved nephrotic contracted kidneys,³¹ that is, contraction following on a genuine or pure nephrosis, that most pathologists have never seen any. Barker's³⁰ suggestion, therefore, that his experimental renal lesions might explain "why most so-called nephrosis cases that escape intercurrent infections, die of uremia and at post mortem show scarred and contracted kidneys" is irrelevant, since most cases of so-called nephrosis, as has been so clearly demonstrated by Bell,⁴⁵ are obvious forms of glomerulonephritis, easily recognized by experienced pathologists, if not by clinicians.

Apart from this question, the more important one arises as to the actual nature of these renal lesions in dogs and their relation to plasmapheresis. So far, Barker's evidence is based on observations made on a few dogs. Even a superficial familiarity with "spontaneous" nephropathy in dogs immediately leads one to question the pathogenesis of these renal changes. Many authors have described "spontaneous" lesions in dogs' kidneys as such or have mistaken them for something they wanted to produce. Long experiments are particularly dangerous, for even a preliminary biopsy, proving the absence of certain lesions, does not rule out the possibility of spontaneous development under laboratory conditions later. This has been well demonstrated in the excellent work of Bell and Hartzell.⁴⁶ The papers of Barker and Kirk present no satisfactory controls.

It is perhaps fortunate that in the present investigation many dogs lived only a short period. Therefore a large series of kidneys was

45 Bell, E. T. *Am J Path* **5** 587, 1929.

46 Bell, E. T., and Hartzell, T. B. *Spontaneous Nephritis in Rabbits and Its Relation to Chronic Nephritis in Man*, *J Infect Dis* **24** 628 (June) 1919.

studied. Some control experiments were carried out. This gives an opportunity to compare the renal lesions in various ways, that is, in relation to the duration of plasmapheresis, to the presence or absence of gross infection in the kidneys and to various control procedures. Renal changes more or less comparable to the advanced stages described by Barker and Kirk were found in two dogs, dog 85, which had been bled only three days, was discarded and died of distemper thirty-two days later, dog 16B died in a state of shock on the second day of a control experiment involving the reinjection of his own citrated whole blood. It is fair to conclude that the experimental procedure could not have produced the extreme fibrosis in the kidneys of these two dogs in such a short time. On the other hand, in dogs 17, 34, 35, 69, 71, 86, 89 and 90, on which vigorous plasmapheresis was performed eighteen, twenty-four, twenty-nine, twenty-four, fifteen, sixty, eighteen and thirty-seven days, respectively, during a total experimental period of thirty-one, thirty-six, forty-seven, thirty-one, twenty-eight, one hundred and thirty-nine, thirty-four, and ninety-eight days, respectively, the renal lesions, apart from infarcts, abscesses and other changes expected with the method used for bleeding, consisted almost entirely of varying degrees of infiltration with mononuclear cells. In fact, in dogs 17, 35 and 69 there were no infiltrates. These perivascular and intertubular collections of "plasma cells," lymphocytes and occasionally polymorphonuclears were also found in the renal cortex of dogs which had died after very short periods of plasmapheresis. Thus dogs 14, 15, 32, 33 and 72 with experimental life periods of only five, six, five, eight and three days, respectively, showed from slight to marked mononuclear infiltration. Are these the result of, or are they related to, hypoproteinemia? One answer to this question is the observation in dog 39C of many linear and wedge-shaped areas of mononuclear infiltration with corresponding atrophy of the tubules. Dog 39C was a control animal transfused for twenty of twenty-nine days with from 200 to 400 cc of other dogs' blood daily. No depletion of plasma was carried out, and the plasma proteins varied between 4.77 and 5.28 per cent during the last eleven days of the dog's life. Another answer is the relatively extensive literature⁴⁷ on more or less identical lesions reported from many parts of the world in connection with work on rabbits, dogs, cattle and cats. This is not the place to discuss the etiologies of such lesions in the kidney. It should be noted, however, that in our experiments vegetative endocarditis was frequent and asepsis was not employed, while Barker and Kirk used careful aseptic technic. The results are difficult to distinguish in the two series. What is most significant, however, is the

⁴⁷ Leiter, L. Experimental Chronic Glomerulonephritis, *Arch Int Med* **33** 611 (May) 1924, Data to be published

complete lack of relation between these acute and chronic truly interstitial nephritides in animals and chronic nephritis in man. This has been pointed out before,⁴⁸ but apparently still needs emphasis in view of the recent confusion. The lack of correlation between low plasma proteins and these renal lesions is self-evident from the few control experiments reported.

It seems from this discussion that the renal lesions following plasmapheresis may have nothing to do with plasmapheresis except so far as dogs are followed over a long enough period to allow for the full development of "spontaneous" lesions or for changes possibly due to the repeated intravenous injection of particulate matter—erythrocytes, more or less damaged by centrifugation, saline solutions and what not. One could not, of course, consider these lesions as a "nephrosis," if one understands by "nephrosis" that form of renal pathology regularly associated with the nephrotic syndrome in man. The fatty changes described in dogs' kidneys are so nonspecific as to be almost physiologic.⁴⁹ Deposition of doubly refractile lipid (cholesterol ester) cannot be found in abnormal amounts in dogs' kidneys, except in calcifying infarcted areas where they are readily demonstrable in masses. This is true in both the long and the short experiments. Here, again, is a striking contrast between the kidneys of dogs with experimental nephrotic edema and the kidneys of patients with "nephrosis" or whatever else it may be called. Experimental edema and "nephrosis" are not synonymous by any means.

SUMMARY AND CONCLUSIONS

Edema has regularly been produced in dogs by adequate plasmapheresis and the resulting reduction in the plasma proteins. The critical level of edema of the plasma proteins is about 3 per cent. Interruption of depletion of plasma is followed by an immediate increase in the plasma proteins and an equally rapid disappearance of edema by diuresis. The disturbance in water balance seems to be largely a temporary upset in the normal equilibrium between the capillary hydrostatic or filtration forces and the plasma protein osmotic or reabsorption forces. It is not primarily dependent on cardiac, renal or capillary permeability factors.

This experimental edema is nephrotic, as demonstrated, for the first time, by actual quantitative analysis of the protein content of the transudates. The low protein content lies exactly within the range

48 Bell, E. T., and Hartzell, T. B. Effect of Foreign Protein on the Kidney, *J. Infect. Dis.* **24** 618 (June) 1919. Bloomfield, A. L. *Bull. Johns Hopkins Hosp.* **30** 121, 1919. Bell, E. T., Clawson, B. J., and Hartzell, T. B. *Am. J. Path.* **1** 247, 1925.

49 Henschen, F. *Acta med. Scandinav.* **53** 774, 1921.

of clinical nephrotic edema fluids and is essentially of the same order of magnitude as the concentration of protein in normal cerebrospinal fluid and of other ultrafiltrates of the plasma

The study of the regeneration of the plasma proteins in the depleted dogs has confirmed the earlier work of Whipple and his associates, which showed that globulin was reformed faster than albumin

The blood cholesterol tended to decrease during vigorous plasmapheresis. With cessation of bleeding, the cholesterol usually rose, occasionally to values considerably above normal. This was, however, only a temporary phenomenon and was in no way suggestive of the hypercholesterolemia of the nephrotic syndrome in man.

Histologic study of the kidneys in these experiments has failed to produce any clearcut evidence to support the contention of Barker and Kirk that hypoproteinemia leads to contracted kidneys. In fact, the control experiments and other facts reported seem to lead directly to the conclusion that Barker and Kirk have erred in two directions. First, they have overlooked the possibility and the frequency of "spontaneous" contracted kidneys in dogs. Second, they have apparently failed to realize the lack of essential resemblance between the so-called renal lesions of plasmapheresis and the histologic changes in the kidneys of patients with so-called nephrosis. In view of this confusion, it becomes evident that experimental nephrotic edema in dogs is not quite the same thing as "experimental nephrosis." Experimental nephrosis has not yet been produced.

The rôle of starvation, of the administration of salt and water by stomach tube and of certain other factors in the experimental procedure has been controlled to a certain degree.

The relation between experimental nephrotic edema and other experimental and clinical edemas has been discussed.

In collaboration with Dr. I. S. Falk, we have presented the first published data on the protein content of the plasma and of the edema fluid in a "spontaneous" nephrotic edema occurring in a monkey.

IS POLIOMYELITIS A DISEASE OF THE LYMPHATIC SYSTEM? *

MONTROSE T. BURROWS, M.D.
PASADENA, CALIF.

It seems important to point out at this time that acute anterior poliomyelitis (infantile paralysis) may not be primarily a disease of the central nervous system, but that it may be more correctly classed with the diseases of the lymphatic systems of the body. The change that is probably common to all cases of this disease is an enlargement or a hyperplasia of some or all of the lymphatic structures of the organism. Those parts most frequently attacked are Peyer's patches and the solitary follicles of the intestines, the mesenteric lymph glands, the retroperitoneal glands, the peribronchial glands, the tonsils, the lymph glands of the neck, the axillae and the groin. In the later stages of any attack one may often make the diagnosis of the existence of the disease through noting a slight but definite enlargement of one or both of the epitrochlear glands.

While the gross enlargement of the peripheral lymphatic glands is often not marked, it is always present to some degree and is one of the necessary diagnostic signs in the mild and abortive cases. This enlargement of the lymphatic tissues is one of the striking peculiarities of all of the cases that come to autopsy. Not only are those lymphatic structures already mentioned involved, but one may also see hyperplasia both grossly and microscopically in the thymus and the malpighian corpuscles of the spleen.

THE LYMPHATICS OF THE CENTRAL NERVOUS SYSTEM

In the central nervous system the lymphatics of the body are represented by spaces which surround the blood vessels. These spaces are known as the perivascular spaces. They empty into the subarachnoid space and in turn are thus connected with the ventricles of the brain. The pacchionian granulations are structures along the sides of the veins through which substances are filtered, probably also from the subarachnoid space into the veins and the general circulation. These perivascular spaces, like the subarachnoid space, are lined by a single layer of endothelial cells. The pacchionian granulations are areas in which this lining endothelium pouches into the walls of the veins.

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* Revised from paper and discussion given before the Pasadena Branch of the Los Angeles County Medical Society, June, 1930.

It is these perivascular spaces and the subarachnoid space that become involved in an attack of true poliomyelitis. There is no evidence to show that the nerve tissue is attacked directly. Apparently it suffers only secondarily from the changes that occur primarily in these spaces and in the meninges.

INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM
(UNCOMMON IN ANY EPIDEMIC)

While there was a time when it was thought that poliomyelitis was a disease primarily of the central nervous system, it is now known that this is not true. The great mass of cases of this disease never show any involvement of the central nervous system. The symptoms designated by the name poliomyelitis are evidently only complications which may occur in a widespread infectious disease the pathology of which has not been clearly presented, and which in its eventual solution will not be found to be strikingly different in its manner of spread from many of the more common infections that occur in epidemics. While some authors have thought that as many as 25 per cent of the cases in an epidemic show no nervous symptoms, others have considered that such mild cases represent as many as from 65 to 75 per cent of all cases of this disease (Parkes and Neal¹). As knowledge of this disease has increased, however, it has become evident that even the latter figures are probably too low.

Before Wickman's² interesting study of an epidemic in Sweden and other studies made in other places, about 1911, the relation between these milder forms of the disease and those in which paralysis occurs was not generally recognized. The earlier work of Caverly, 1894,³ had made no impression. It was only after Flexner and Lewis⁴ and others had shown it to be a true infectious disease, the virus of which passes readily through a Berkefeld filter, that the manner of its transmission became a problem of general interest. The cases of paralysis or true poliomyelitis were generally widely separated, and it was natural to suspect even then that the virus was carried in some peculiar manner by some animal, insect or other agent. It was difficult to conceive that the

1 Parkes, W. H., and Neal, Josephine B. Poliomyelitis. A Brief Resume of the Epidemiology, Symptomatology and Treatment, *Southwestern Med* **11** 523 (Dec.) 1927.

2 Wickman, Ivar. Acute Poliomyelitis (Henne-Medén's Disease), translated by W. J. M. A. Maloney, monograph 16, New York, J. Nerv. & Ment. Dis. Publ. Co., 1913.

3 Caverly, C. S. History of an Epidemic of Acute Nervous Disease of Unusual Type, *New York M. Rec.* **46** 673 (Dec.) 1894.

4 Flexner, S., and Lewis, P. A. The Transmission of Epidemic Poliomyelitis to Monkeys, *J. A. M. A.* **53** 1913 (Dec. 4) 1909.

paralysis is as Amoss⁵ termed it only a "complication" and often a rare complication in a widespread infectious disease which, without involvement of the central nervous system is so mild that it never leads to death and is often difficult to distinguish from other mild forms of gastro-intestinal disturbance. Since 1913 it has become more and more apparent however that this is true but even now there is a tendency to class this disease as one primarily of the central nervous system rather than in the light of its true pathology. Attention is being centered too much on the rare cases in which paralysis occurs, rather than on the hundreds of mild cases that may be wholly responsible for the spread of the infection. Too many deductions are being drawn from studies on monkeys in which the virus has been introduced directly into the brain or some site chosen by the operator, rather than from the clinical cases in which the natural routes of infection and spread of the disease can be followed more accurately.

MATERIAL

While the study of poliomyelitis and similar infectious diseases is quite removed from my chief endeavors in medicine at this time, it was my good fortune to have played an active part in the attempt to combat and study this disease in the epidemic that existed in the city of Baltimore in the summer of 1916. It was possible at that time not only to study the clinical aspects of the disease its epidemiology, its treatment and its bacteriology but also to obtain excellent pathologic material. By police order, the city granted an autopsy on every fatal case. As acting resident pathologist of Johns Hopkins Hospital, I performed most of these autopsies myself. In each instance a complete autopsy was performed, and all the organs were studied not only for the gross, but for the microscopic, changes.

These autopsies, together with a rather extensive clinical investigation of the disease have given an opportunity to correlate more carefully the clinical course of the disease with the pathology, and to obtain a point of view somewhat different from that held by those who look at the disease largely as a primary poliomyelitis rather than a systemic disease that may have a central nervous complication.

I have already reviewed briefly the pathology of this disease in an attempt to separate it from epidemic encephalitis⁶ and to find the differential pathologic peculiarities of the latter affliction. The correlations of the pathologic symptoms and signs with the clinical symptoms have not been published. It seems important to present them now.

5 Amoss, H. L. Poliomyelitis. *South M. J.* **23**: 18 (Jan) 1930.

6 Burrows, M. T. Neuritis of the Cranial Nerves in Lethargic Encephalitis and the Differential Anatomic Diagnosis Between It and Acute Poliomyelitis, *Arch. Int. Med.* **26**: 477 (Oct.) 1920.

When my associates and I commenced work on the epidemic of poliomyelitis in Baltimore in 1916, we believed definitely that it was a primary disease of the central nervous system, and we were in no way convinced that the paralysis was only a rare complication that might occur in any epidemic. At the end of the epidemic it became clear, however, that our first assumption was not true. Not only from the rarity of the paralysis in this epidemic, but also from the study of the pathology, it became certain that the nerve tissue is not attacked directly, but suffers only from changes in the perivascular spaces, and that in any epidemic these spaces are only rarely involved to any great extent. In the great mass of cases existing in this epidemic, there were only a few patients who ever suffered from any noticeable symptoms of the nervous system. When paralyzes did occur, the lesions were not primarily in the nerve tissue, but in the perivascular spaces and the subarachnoid space. The latter fact had already been described in the pathologic studies of Peabody, Draper and Dochez.⁷

PATHOLOGY

Gross Pathology—The pathologic picture in all of the fatal cases was a general lymphoid hyperplasia which was most marked in the solitary follicles of the gastro-intestinal tract, Peyer's patches and the mesenteric lymph nodes. In each of the fatal cases the disease began as in the milder ones with fever, gastro-intestinal disturbance, headache and eventual paralysis, which had its origin always in some part of the spinal cord. No death could be attributed to toxic symptoms. Death intervened only when the respiratory center became involved and was eventually the direct result of respiratory paralysis.

In the milder cases only headache, fever and gastro-intestinal disturbances of various degrees were observed.

Portal of Entry in the Gastro-Intestinal Tract—These general facts led us to believe that the disease begins primarily in the lymphatics of the gastro-intestinal tract and spreads from thence to the lymphatics of other parts. In the less resistant cases it may spread to the subarachnoid space and the perivascular spaces of the spinal cord, medulla and adjacent parts. Wickman² thought that it arose in the intestines. Flexner⁸ and his students, from the studies of infected monkeys, looked at the nasal passages as the possible portal of entry. In the clinical cases that I observed it was rare to find any very prominent symptoms

⁷ Peabody, F. W., Draper, G., and Dochez, A. R. A Clinical Study of Acute Poliomyelitis, Monogr. Rockefeller Inst. M. Research, New York, 1912.

⁸ Flexner, S., and Amoss, H. L. Persistence of the Virus of Poliomyelitis in the Nasopharynx, J. Exper. Med. **29** 379, 1919.

in the nose and throat and more recently Amoss and Taylor⁹ have isolated substances from the secretions of the nasal passages of healthy monkeys that neutralize the virus of this disease

Microscopic Pathology—Microscopic examination of the lymph glands shows either a decrease in the blood supply or a dilatation and congestion of the capillary bed a mild edema which gives the gland a firm resistance and a most active proliferation of the lymphoid cells. The gland becomes a solid mass of lymphocytes or small mononuclear cells. The sinuses are not clearly made out but the germinal centers of

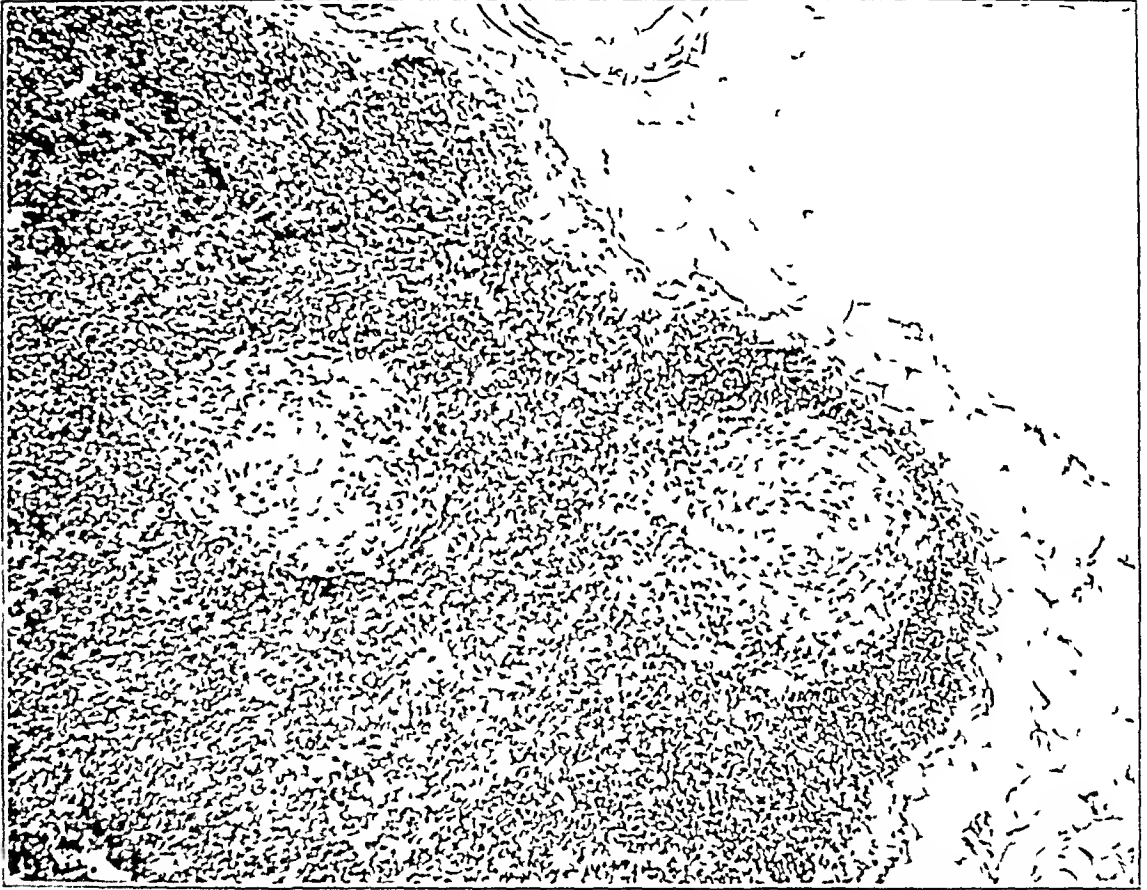


Fig. 1—A part of a section of a mesenteric lymph gland in a white boy, aged 3½ years. The child was sick for five days, dying of respiratory paralysis. The section shows the large clear centers of the follicles and the proliferation of lymphoid cells peculiar to the condition.

the follicles stand out as prominent clear areas. These centers show few cells but much cellular debris. There are numbers of mitoses near their peripheries and a few in their more central parts. This growth may proceed to actual necrosis of the centers of these follicles. There is also an active proliferation of the endothelial cells lining the sinuses and other parts of the gland. The picture is that of a true hyperplasia.

⁹ Amoss, H. L., and Taylor, E. Neutralization of the Virus of Poliomyelitis by Nasal Washings, *J. Exper. Med.* 25: 507 (April) 1917.

These changes in the lymphatics become most marked in Peyer's patches, the solitary follicles of the intestines and the mesenteric lymph nodes. These follicles and Peyer's patches are easily seen grossly when the intestines are opened. They are enlarged and raised well above the surface of the surrounding mucous membrane (fig 2). They show the same picture microscopically as that described for the lymph glands.

While in the fatal cases the enlargement of the lymphatics is most marked in all parts of the body, the mesenteric lymph glands are generally the larger. The malpighian corpuscles of the spleen are prominent on the cut surface of this organ. The peribronchial lymph glands, the lymph glands of the neck, axillae, groin and other parts and the adenoid tissue of the nose and throat and the thymus show this same hyperplasia.



Fig 2—The surface of the ileum in a white boy, aged 6½ years. The boy was sick for five days, including an intermission. The figure shows typical hyperplastic Peyer's patches peculiar to this disease.

both grossly and microscopically. While the tonsils were noticeably enlarged in a few cases, it was rare to find them showing the strikingly gross hyperplasia presented by the lymphoid tissue of the gastrointestinal tract.

Changes in the Nervous System—The changes in the nervous system were of a similar nature. A primary involvement of the nerve tissue does not exist apparently. The nerve tissue shows changes that are secondary to those existing in the lymphatic channels of this tissue. The primary changes appear to be always in the perivascular spaces and the subarachnoid space. The microscopic picture noted in the subarachnoid space is an active proliferation of the endothelial lining cells following congestion and edema. Many of these cells loosen

and appear as lymphoid cells in this space (fig 3). Within the nerve tissue, the primary changes are in the perivascular spaces. These spaces become distended with fluid. Then endothelial lining cells proliferate. The edema may become excessive, rupturing the lining membrane, and death may intervene early from this edematous distention alone, if the medulla or the respiratory center is involved (fig 4).

In other cases, especially in those in which the congestion and edema of the spinal cord persist for a longer time, other changes most often intervene. There is a much greater proliferation of the endothelial



Fig 3—A part of a section of the cervical region of the spinal cord and meninges of a white boy, aged $3\frac{1}{2}$ years. The boy was sick for five days and showed only mild meningeal symptoms. The section shows the characteristic changes in the subarachnoid space.

lining cells (fig 5). The surrounding glia cells may also proliferate and, eventually, areas of necrosis of the nerve tissue result. It is only in the latter areas of necrosis that one ever sees polymorphonuclear cells.

Such abscesses occur always in the immediate vicinity of the blood vessels (fig 5), and there is considerable variation in the general architecture of the lesion in the different cases. In certain cases there are no marked early changes in the nerve cells, but the proliferation of the

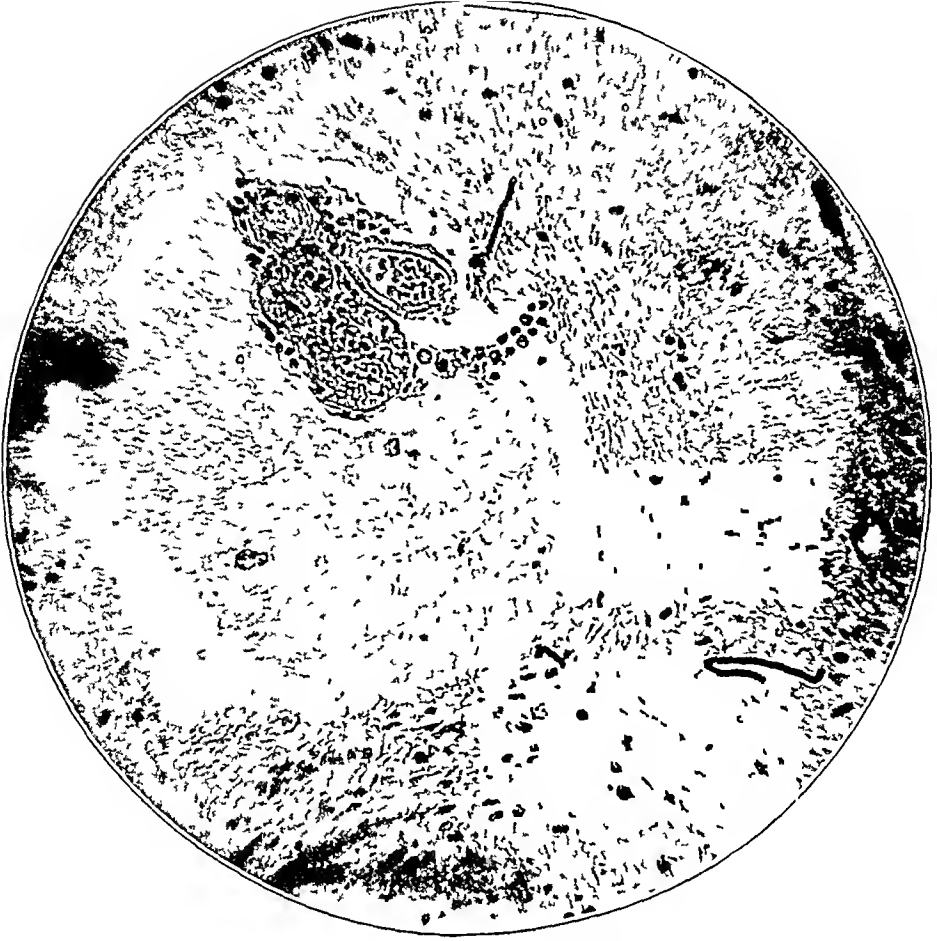


Fig 4—A vessel in the anterior horn of the cervical portion of the spinal cord, showing an excessive accumulation of fluid about it and rupture of the perivascular space. The section was taken from a child 2 years and 9 months old who had been sick with the disease for three days, and who died in a convulsion. This child gave a positive Kernig sign.



Fig 5—A section of the lumbar region of the spinal cord in a colored girl, aged 5 years, who had been sick for four days and had paralysis of the leg for at least forty-eight hours before death. The figure shows secondary changes in the nerve cells and necrosis and the formation of abscesses about a few of the perivascular spaces.

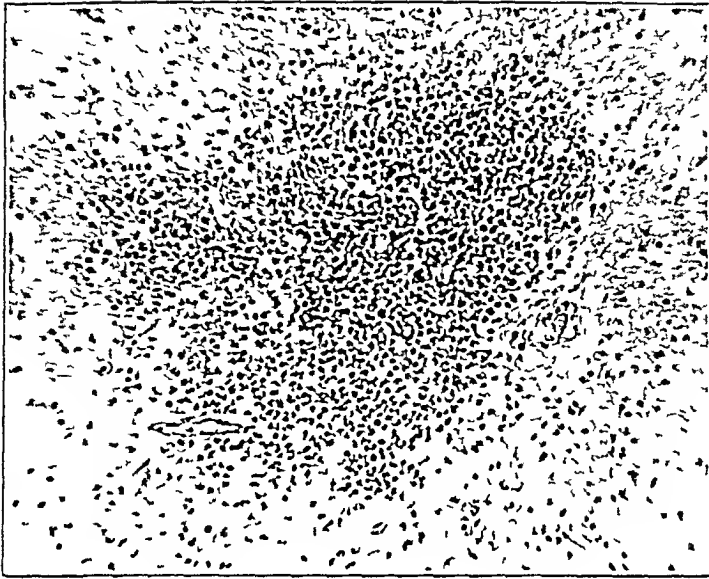


Fig 6—Blood vessels of the lumbar region of the spinal cord in a white boy, aged 3 years. The child had been known to be sick for only three days. The section shows an excessive proliferation of endothelial cells about several of the smaller blood vessels.

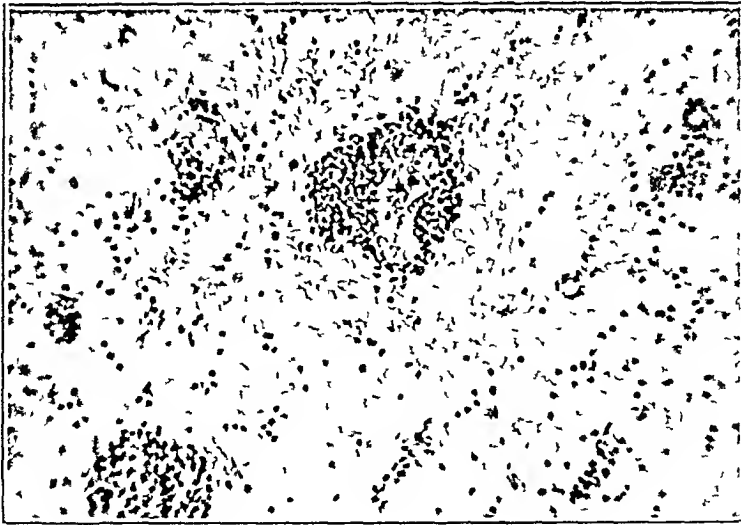


Fig 7—Vessels in a section of the cervical region of the spinal cord in a colored girl, aged 4 years, who had been sick for five days. The upper extremities of this child had been paralyzed forty-eight hours before death. The section shows an active proliferation of the endothelial cells of the perivascular spaces without edema and some proliferation of the glia cells.

endothelial lining cells of the perivascular spaces becomes excessive. These cells not only distend the space, but they spread to fill the adjacent nerve tissue (fig 6). In other cases the spaces merely become distended with these cells, the cell breaking the wall of the space at only a few places (fig 7). The glia cells may or may not show evidence of proliferation in either of these types.

In a third group, the picture may be different. The proliferating endothelial cells migrate directly into the nerve tissue. The space is often devoid of fluid. The nerve tissue about the vessel shows fatty changes, and there is an evident proliferation of the adjacent glia cells (fig 8).

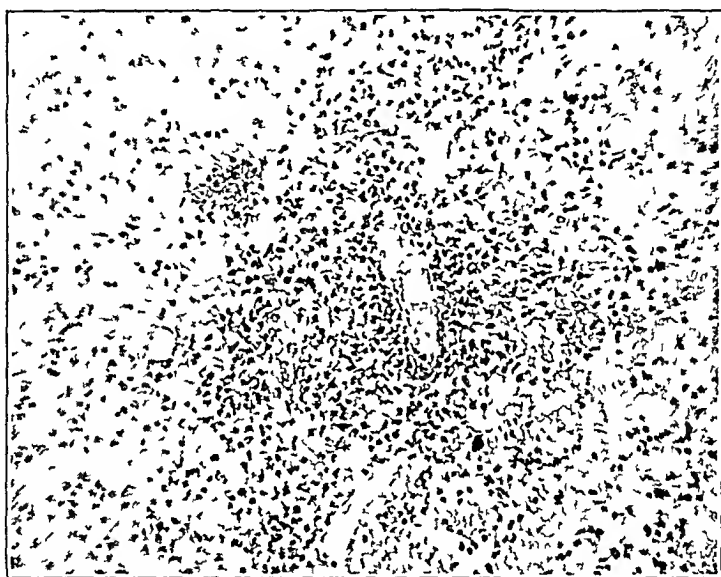


Fig 8—A section taken from the cervical region of the spinal cord of a white boy, aged $7\frac{1}{2}$ years, who had been sick for five days, including a remission. The upper extremities of this child were paralyzed two and a half days before death. The proliferating endothelial cells have migrated into the nerve tissue. The nerve tissue shows fatty changes, and there is very evident proliferation of the glia cells.

While Hurst¹⁰ has tried to show that the primary lesions of the central nervous system are in the nerve cells rather than in the lymphatic channels, it seems evident that he drew these conclusions because he was looking at the end-result of a chain of pathologic processes rather than at the primary lesion. He did not study the disease in man but in monkeys, and in monkeys that had been inoculated with the virus and in many of which this virus had been introduced directly into the central nervous system. Monkeys are very susceptible to the virus, and the destruction is often much more marked in their nerve tissue than in

10 Hurst, E. W. The Histology of Experimental Poliomyelitis, *J. Path. & Bact.* **32** 457, 1929.

that of human beings. Any evidence of a primary destruction of the nerve cells was absent in our case, and a careful survey of Hurst's description disproves his deductions. The lesions that he described in the brain at the border of the chief parts involved showed only involvement of the perivascular spaces and no change in the nerve cells.

Clark and Amoss¹¹ had already shown that when monkeys are infected by an intraspinal injection, the meninges may become infected without paralysis, showing, as they stated, that the changes in the interstitial tissue in the meninges, blood vessels and ground substance play a determining part.

A Disease of the Lymphatic Tissues—It seems quite evident, therefore, from all available evidence at the present time that the primary lesions of the poliomyelitis are not in the central nervous system. Poliomyelitis is probably a misnomer as it is applied to the disease as a whole. It is merely a complication of a widespread infectious disease. This disease is not a primary disease of the central nervous system; it is a disease of the lymphatic systems of the body. The lesions presented are not of the kind in which pus appears early, but the lesion is rather that of an acute hyperplastic lymphadenitis.

While it is possible that the disease may be made to enter monkeys by way of the nasal passages, in the greater number of cases in man the disease enters apparently by way of the intestinal or gastro-intestinal tract. Clinically, in the great majority of cases, the disease begins as a gastro-intestinal upset, and pathologically, the most pronounced lesions are usually found in the solitary follicles and Peyer's patches of these parts. From these lymphatic structures it spreads to other parts of the body until the immunity of the patient overcomes its activity. At the present time, the great majority of persons recover after a small involvement of these tissues, while in others the lymphatics throughout the entire organism become involved, and paralysis or death may intervene.

DIFFICULTIES ENCOUNTERED IN COMBATING THE DISEASE

Inadequacy of Present Methods of Quarantine—I bring these facts forward because it seems that the present general attitude and methods of quarantine can have little influence in stopping the spread of this infection. Poliomyelitis, as it is now termed, is probably always present as a sporadic disease, and it appears in epidemic form as often as it is carried into isolated districts or a new crop of children develops in the older communities. This deduction has been borne out not only by clinical studies, but by recent experimental evidence. Paralyses are more common in the northern than in the southern parts of this country.

¹¹ Clark, P. F., and Amoss, H. L. Intraspinal Infection in Poliomyelitis, *J. Exper. Med.* **19** 217, 1914.

Epidemics are more common in the cities than in the country Aycock and Kramer¹² studied the blood of adults in both urban and rural populations, who, so far as they knew, had never had the disease The blood of these persons was tested on monkeys for their ability to neutralize a virulent virus The blood of as many as 69 per cent of those from the cities neutralized the virus, while only 20.7 per cent of those from country districts showed the existence of such immune bodies In the same manner, these authors¹³ studied the blood of adults from cities in the South They found as many immune there as in the North, showing

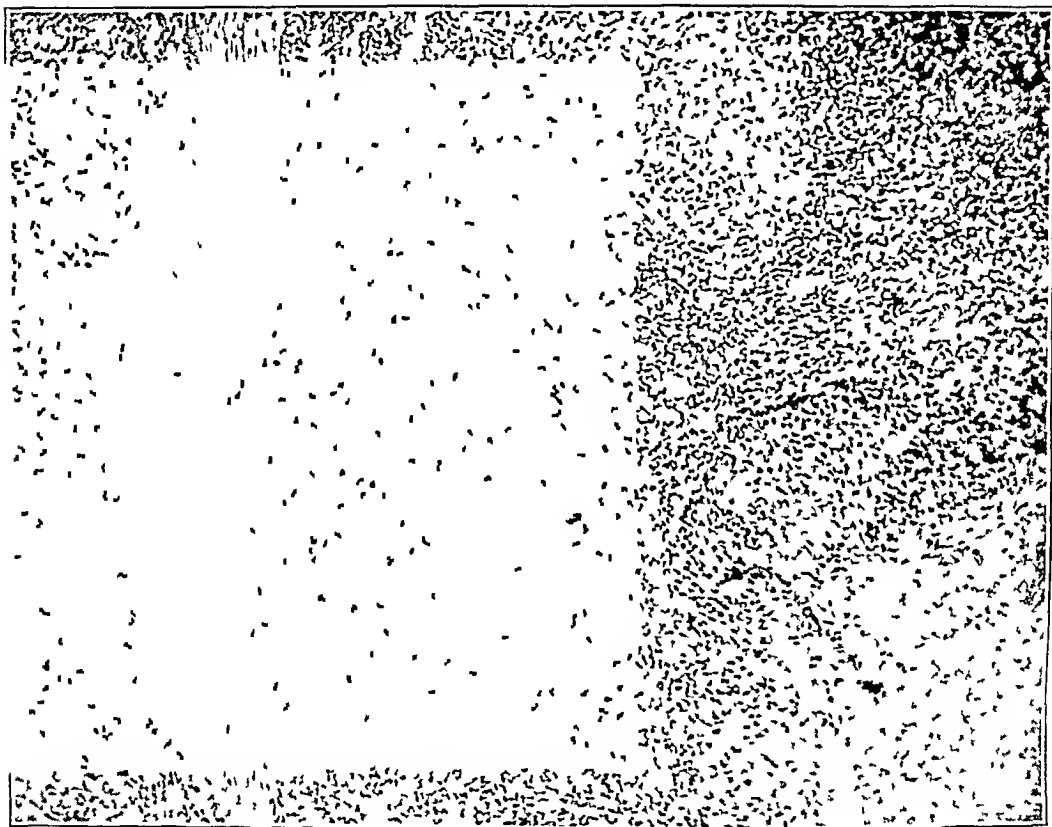


Fig 9—A section of the tonsil of a white boy, aged 6½ years, who had been sick for four days It shows the typical hyperplasia seen in other lymphoid tissues of the body

that the disease must exist there as elsewhere, but that fewer show complications of the central nervous system

It thus becomes evident that if this disease is to be eradicated from the community, it must be attacked in a manner different from that used

12 Aycock, W Lloyd, and Kramer, S D Immunity to Poliomyelitis in Normal Individuals in Urban and Rural Communities as Indicated by the Neutralization Test, *J Prev Med* 4 189 (May) 1930

13 Aycock, W Lloyd, and Kramer, S D Immunity to Poliomyelitis in a Southern Population as Shown by the Neutralization Test, *J Prev Med* 4 201 (May) 1930

at the present time. It is evidently a widespread infection. To protect any person against it would necessitate complete isolation throughout his entire life. As Frost¹⁴ pointed out, the cases in which paralysis occurs are generally widely separated, and it is of little use to quarantine these patients while there are probably hundreds of others at large carrying germs as virulent as do those who have suffered permanent disability.

Infantile Paralysis a Misnomer—The name infantile paralysis is also misleading. While it is true that children are most often attacked, 90 per cent of the cases appearing probably in children from 1 to 10 years of age (Parkes and Neal¹), adults are not immune unless they have already come in contact with the virus. The high incidence in children is probably due only to the fact that the disease is most contagious and very widespread. It is similar to measles in this regard. Most adults escape in any epidemic because they have suffered from the disease at a previous time. One attack seems to be ample to produce immunity. Frost¹⁴ noted in an epidemic in New York City that sixty-five children to one adult were affected. In the epidemic in Iowa, on the other hand, where the population is more scattered and the chances of previous infection are less, there were only six children sick to one adult.

Difficulty of Diagnosing Mild Cases—The difficulty of following accurately the course of any epidemic of poliomyelitis is the mild character of most cases and the difficulty of distinguishing them from any other form of gastro-intestinal disturbance. In a careful study of an epidemic in an apartment house in Baltimore, which Park and I were able to make in 1916,¹⁵ we found that every child became ill who had previously come in contact with the first child infected or with others infected from him. While there seemed to be little doubt that each of these children had the disease, it would have been difficult to prove its existence in many of them if others had not shown involvement of the central nervous tissue.

This difficulty of making a diagnosis in the mild forms of the disease, yet the evident widespread character of the infection, is well illustrated in the recent epidemic in California. A large number of cases of gastro-intestinal infection existed in the small vicinity about my own residence. Two of my own children became ill with headache, vomiting and fever, the indisposition lasting one day in one case and two days in the other. The wife of a neighbor, a woman 31, had been ill nine days previously with vomiting and headache. She recovered in a few days. Three days

¹⁴ Frost, W. H. The Epidemiology of Poliomyelitis, J. Iowa M. Soc. **19** 223 (May) 1929.

¹⁵ Burrows, M. T., and Park, E. A. The Study of a Small Outbreak of Poliomyelitis in an Apartment House, Occurring in the Course of an Epidemic in a Large City, Arch. Int. Med. **20** 56 (July) 1917.

after the onset of her trouble, her husband became ill with something peculiar to his experience. The onset of his illness was sudden. His temperature rose to 102.5 F, and he suffered from a severe and peculiar headache. They had been patients of mine, and I was called to see him. The history revealed an obstinate constipation, also. The examination showed very little or no coating of the tongue, but slight enlargement of the cervical, inguinal, axillary and epitrochlear glands. The abdomen was slightly distended, but one could with slight pressure feel small gas pockets over the whole of it. A diagnosis of poliomyelitis seemed most logical. A saline cathartic was ordered.¹⁶ The temperature went down promptly. The patient was quite ill for five days, and he remained weak and exhausted for another twelve days.

COURSE OF THE DISEASE

Period of Incubation—In this small epidemic about my own residence in California, the period of incubation was, I calculated, from three to five days. Aycock and Luther¹⁷ gave the period of incubation as from six to twenty days. In the apartment house in Baltimore, where all contacts could be followed carefully, Park and I¹⁵ concluded that the period of incubation was from three to seven days.

Paralysis, a Complication—While it is true that infectious diseases of all types exist in a mild form in many persons and that others apparently escape them entirely, the picture in poliomyelitis is somewhat different. The disease always begins as a systemic disturbance. The great majority of the cases are mild. Paralysis is evidently a rare occurrence. The paralysis thus appears to be a complication rather than a primary part of the condition. It is similar to the nephritis that may complicate scarlet fever. While the symptoms of the central nervous system may follow the systemic symptoms at once in a few cases, there is generally a remission between the systemic symptoms and the paralysis.¹⁸

Transmission—The disease is probably transmitted from patient to patient by direct contact. The germs may be carried in the mouths of

16 Edema is one of the striking changes in the tissues in this disease. Salts are indicated because the treatment should be directed toward relieving this edema and the resulting pressure. Aycock and Amoss have noted some results after the injection of hypertonic solution of salt together with serum in an attempt to cure the disease in monkeys. (Aycock, W. Lloyd, and Amoss, H. L. Experiments on Local Specific Therapy in Poliomyelitis. Utilization of Hypertonic Solutions in the Serum Treatment of Experimental Poliomyelitis, Bull. Johns Hopkins Hosp. 34: 361 [Nov.] 1923.)

17 Aycock, W. Lloyd, and Luther, Eliot H. The Incubation Period of Poliomyelitis, J. Prev. Med. 3: 103 (March) 1929.

18 Peabody, Draper and Dochez (footnote 7). Leake, J. P. The Diagnosis of Poliomyelitis, Pub. Health Rep. 32: 1831 (Nov. 2) 1917.

healthy persons¹⁹ as well as in the mouths of patients. Patients harbor the germs for at least several days after having apparently recovered completely. Paik and I found what appeared to be evidence of the germs in the mouth of one patient nineteen days after complete recovery. There was no evidence of the disease in the nasal and pharyngeal washing of this patient and of another patient thirty-five days after they had recovered from the disease (Burrows and Paik¹⁵).

Prevalence—As I have already stated, poliomyelitis is evidently as widespread as any infectious disease. It is evidently present at all times in thickly populated districts and occurs in epidemic form as soon as a new crop of children of considerable number develops in that district. In many of the larger eastern cities these epidemics occur more or less regularly every two to six years, and the high incidence is in children from a few months to 6 years of age. The question of escaping paralysis is evidently a question of one's resistance to the disease.

In the epidemic of 1916, as many cases in which paralysis occurred existed as in any epidemic. Even in this epidemic we calculated that within the field of our observation there were 1,500 cases in which paralysis occurred, 250 in which it did not occur and 50 cases terminating in death. In the cases that we studied we found a group of children well isolated for a time from the infection. The disease was introduced to one family finally, however, by an adult carrier. Every child in the apartment house who came in contact with this family or with children who had made this contact became ill, while those who did not make these contacts remained well.

In this particular isolated group, only two of the twelve children who were ill became paralyzed. Muscular weakness was present for a time in a few, others showed meningeal symptoms, and others only headache, fever and gastro-intestinal disturbance of short duration.

CLINICOPATHOLOGIC CORRELATIONS

In the cases that came to autopsy the pathologic changes were as I have outlined them. There was a general lymphoid hyperplasia reaching its maximum in Peyer's patches, the solitary lymph follicle of the gastro-intestinal tract and the mesenteric lymph nodes. In many of the cases, no lymphoid tissues escaped except perhaps the perivascular spaces of the brain itself, in others, the spread was more irregular and patchy. Only a part of the lymphoid tissue was involved, and only parts of the spinal cord, pons and medulla showed changes.

¹⁹ Flexner, S., Clark, P. F., and Fraser, F. R. Epidemic Poliomyelitis. Fourteenth Note. Passive Human Carriage of the Virus of Poliomyelitis, J. A. M. A. 60 201 (Jan 18) 1913.

Careful clinical studies have divided the cases into several groups. One classification that may be given is as follows:

Mild	Meningeal	Ataxic
Abortive	Paralytic	Cerebral
	Landry's	

No cerebral type of case was encountered by us in the Baltimore epidemic or elsewhere, although such types have been described in other epidemics. Ataxic types, on the other hand, were seen. In the fatal cases that came to autopsy we found no involvement of the cerebral or cerebellar cortices. The basal nuclei of the brain also showed no evidence of the disease, while the dentate nucleus of the cerebellum was involved in about one third of the cases. We were inclined to believe, therefore, that the ataxia in certain cases might indicate an involvement of this nucleus without injury to the respiratory center.

The ganglions of the dorsal roots of the spinal and the cerebral nerves frequently showed changes, while the nerves themselves were always free from inflammatory changes. In the three cases of epidemic encephalitis that I studied,⁶ the picture was different. There was involvement of the cerebral cortex and the basal nuclei of the brain. The cranial nerves also always showed inflammatory changes. These peculiarities separated the cases of epidemic encephalitis from poliomyelitis.

As Leake¹⁸ clearly pointed out, the systemic changes that are present in all cases are fever, headache and gastro-intestinal disturbances. The latter disturbances, which have been noted most often, are constipation and slight distention. Diarrhea has been seen in certain epidemics, however. Sore throat may be present but it is not common, as are the gastro-intestinal symptoms. The common picture seen at the onset of the disease in this country has been headache, fever (generally pronounced), constipation and vomiting.

We found the tonsils involved in all fatal cases, but this involvement was not as pronounced as that seen in the Peyer's patches and the solitary follicles of the intestines. The tonsils showed microscopically the same hyperplasia, however, as that seen in other lymphatic tissue (fig. 9).

In more than half of the fatal cases in which I performed an autopsy the whole of the spinal cord showed pathologic changes. These changes were most advanced in the lower part of the cord. The picture in these cases was that of Landry's paralysis. In the other cases, the lesions were focal, one part of the cord being involved in one case and another in others. The muscles most frequently involved in the nonfatal cases were the gastrocnemius in the legs and the deltoid in the arms. Death intervened in two of the fatal cases apparently from an immediate involvement of the upper cervical cord and the medulla.

As Leake¹⁸ also pointed out, the meningeal symptoms when present are not so pronounced as those seen in tuberculous and other infections.

of the meninges. One might draw this conclusion from a comparison of the pathologic pictures alone. The patients in the epidemic in Baltimore who showed marked meningeal symptoms and who succumbed later and were brought to autopsy were found to have been suffering from tuberculous meningitis.

SUMMARY

While the exact portal of entry of poliomyelitis is not known, from the clinical and pathologic studies available it seems that the disease must enter by way of the gastro-intestinal lymphatics (Peyer's patches and the solitary follicles). Symptoms in the latter region are always present, while symptoms in the throat are not common. From this portal of entry the disease spreads to contiguous lymphatic tissues in the body. In the mild cases, immunity and recovery result after a limited amount of this tissue is involved. In the less resistant cases, wider extension results, even to the involvement of the lymphoid structures of the central nervous system.

In this regard the disease resembles other infectious diseases. When a number of persons are infected, for instance, with streptococcal sore throat, in one the disease ends after an involvement of the throat alone, in another it spreads from the throat to the larynx and trachea, in another to the bronchi, and in others pneumonia and death result. So in infantile paralysis, it appears that, in the great mass of cases, immunity develops with involvement of small parts of the peripheral lymphatic tissue, in others, more of this tissue is involved, so that one may palpate the cervical, axillary, inguinal and even the epitrochlear and popliteal lymph glands, in still others, the infection spreads to the lymphatic structures of the nerve tissue.

While there was a time when it was thought that poliomyelitis was peculiar in that cases of it are often widely separated, it has now become known that this is not true. It is evidently only a complication in a widespread infectious disease. Most persons show a striking resistance to this infection. An involvement of the gastro-intestinal lymphatics alone is the picture seen in most of them. Many others do not show these symptoms to an extent sufficient to stop their ordinary pursuits of life.

It is in the light of these facts and the pathology as it is known that I have suggested that the name infantile paralysis be changed. It is possible that such a change in the name and the new attitude that it may create will lead to a more rapid advance in the knowledge of the nature of the disease. Such a change in name may also create a more understanding attitude toward it on the part of the laity and correct some of their false impressions. At the present time the methods of quarantine are evidently inadequate and probably quite useless in most instances.

Since it appears that this disease is as widespread as measles, and since the great majority of cases are mild, it does not seem likely that a sufficient number of cases can be recognized to stop any epidemic by quarantine. It is evident, therefore, that other methods must be devised. It seems necessary from the clinical and pathologic studies already made that some method be devised by which the resistance of the whole population can be raised. Some method of vaccination or inoculation such as that used in diphtheria may be the means by which the hideous aspects of this disease can be removed. A mild infection with poliomyelitis seems to leave no bad effects. It is the paralysis or paralysis and death that await the few in every community that must be guarded against.

CONCLUSIONS

1 The pathology of poliomyelitis has been described as studied in a series of about fifty autopsies.

2 The present-day attitude of students of the clinical aspects of this disease has been reviewed with certain original observations.

3 The name acute lymphatic hyperplasia has been suggested for this disease in order that all cases may be properly included under the name. The names "infantile paralysis" and "poliomyelitis" designate only a few of the cases existing at any time in the community.

4 Evidence is brought forward to show that the present methods of quarantine are inadequate. Some method of inoculation or some other measure must be devised to raise the resistance of the whole population if the few are to escape paralysis and death from it.

94 North Madison Avenue

EXPERIMENTAL EDEMA ¹

SAMUEL A. SHELBURNE, M.D.

DALLAS, TEXAS

AND

WILLIAM C. EGLOFF, M.D.

LOS ANGELES

The Starling hypothesis, which holds that the exchange of water between the blood and the tissue fluids through the capillary wall is determined by a delicate balance between the hydrostatic pressure in the capillaries and the osmotic pressure of the plasma proteins, has been almost definitely established by research work, both experimental and clinical. In 1926, Landis² measured the capillary pressure by introducing the micropipet into the capillaries of the mesentery of the frog, and found a gradient of pressure ranging from 14.5 cm. of water at the arterial end to 10 cm. at the venous end. He found that filtration outward occurred when the pressure was above 11.5 cm. of water. White³ found the osmotic pressure of the plasma proteins of the frog to be from 10 to 12 cm. of water. Recently Landis³ (1930) measured the capillary blood pressure in human skin and found that it ranged from 32 mm. of mercury in the arteriolar limb to 12 mm. of mercury in the venous limb. The osmotic pressure of plasma proteins in man ranges from 23 to 28 mm. of mercury. Leiter⁴ (1928) added further evidence when he produced edema by lowering the plasma proteins of dogs. This was accomplished by the selective removal of the plasma (plasma-pheresis). Similar observations were published by Barker and Kirk⁵ (1930).

The clinical evidence has been of no less value. Csataiy⁶ (1891) noted that there was a decrease in the plasma proteins in some patients with nephritis and that the albumin was lowered more than the globulin. These observations were confirmed by Linde, Lundsgaard and Van

¹ Submitted for publication, Oct. 16, 1930.

² From the Medical Clinic of the Peter Bent Brigham Hospital and the Medical Laboratories of the Harvard Medical School.

1 Landis, E. M. The Capillary Pressure in Frog Mesentery as Determined by Micro-Injection Methods, *Am. J. Physiol.* **75** 548, 1926.

2 White, H. L. On Glomerular Filtration, *Am. J. Physiol.* **68** 523, 1924.

3 Landis, E. M. Micro-Injection Studies of Capillary Blood Pressure in Human Skin, *Heart* **15** 209, 1930.

4 Leiter, Louis. Experimental Edema, *Proc. Soc. Exper. Biol. & Med.* **26** 173, 1928.

5 Barker, M. H., and Kirk, E. J. Experimental Edema, *Arch. Int. Med.* **45** 319 (March) 1930.

6 Csataiy, A. Ueber Globulinurie, *Deutsches Arch. f. klin. Med.* **48** 358, 1891.

Slyke⁷ (1924), as well as by others. With Starling's hypothesis in mind, Epstein⁸ expressed the belief that the edema in nephrosis is due to the low plasma protein, and he introduced the diet high in protein to correct this deficiency. This work was confirmed by Moore and Van Slyke⁹ (1903).

We started the experiments reported here with the purpose of producing edema by plasmapheresis in order to study the effect of electrolytes on edema. We adopted essentially the method used by Barker and Kirk⁵ in this laboratory last year. This method of bringing about edema depends on the daily removal of a large amount of blood plasma. Reaccumulation of the plasma protein is prevented by giving a diet deficient in protein. As a result of this reduction in plasma proteins, the osmotic pressure which these proteins exert falls below the capillary pressure, and fluid passes into the tissues. Experiments on three dogs are reported here. The dogs were fed a diet low in protein but adequate in carbohydrate and fat (diet A)¹⁰. The first dog (dog 1) was used purely as a control on the diet, but after a long period on this diet, the plasma proteins fell so low that the addition of salt and water administered by stomach tube precipitated a massive edema. Edema was produced by diet and plasmapheresis in the other two dogs (dogs 2 and 3). The action of various salts on both types of edema was studied. A comparison is drawn between the pathologic and chemical observations in these two types of edema.

PRODUCTION OF EDEMA IN A DOG BY A DIET LOW IN PROTEIN BUT ADEQUATE IN CARBOHYDRATE AND FAT

Schittenhelm and Schlecht¹¹ studied the edema of malnutrition and found the serum proteins low. Denton and Kohman¹² (1913) found

7 Linder, G. C., Lundsgaard, C., and Van Slyke, D. D. The Concentration of the Plasma Proteins in Nephritis, *J. Exper. Med.* **39** 887, 1924.

8 Epstein, A. A. Concerning the Causation of Edema in Chronic Parenchymatous Nephritis. Method for Its Alleviation, *Am. J. M. Sc.* **154** 638, 1917.

9 Moore, N. S., and Van Slyke, D. D. The Relationships Between the Plasma Specific Gravity, Plasma Protein Content and Edema in Nephritis, *J. Clin. Investigation* **8** 337, 1930.

10 Diet A	Grams	Calories	Protein	Total Base	Chlorides
Baked potato	50	42	1.10	0.246	0.019
Cream	50	193	1.25	0.128	0.040
Turnip	200	41	2.60	0.950	0.041
Butter (unsalted)	25	199	0.25	0.028	0.030
Lactose	60	240			
		715	5.20	1.352	0.130

11 Schittenhelm, A., and Schlecht, H. Ueber Oedemkrankheit mit hypotonischer Bradykardie, *Berl. med. Wchnschr.* **55** 1138, 1918.

12 Denton, M. C., and Kohman, E. A. Feeding Experiments with Raw and Boiled Carrots, *J. Biol. Chem.* **36** 249, 1918.

that edema developed in rats fed on carrots Frisch, Mendel and Peters¹³ (1930) confirmed these experiments and revealed that the total plasma proteins were low in their rats They also made clear that vitamin deficiency played no part in the edema produced in this way We have been unable to find any reference to the production of edema in dogs by the use of diets deficient in protein

Dog 1 was chosen at the beginning of our experiments as a control animal for a diet which would be most favorable for the production of edema by plasmapheresis However, after she had been fed this diet for eighty-eight days, the plasma proteins fell so low that we were able to precipitate massive edema by the addition of large amounts of water and sodium chloride by stomach tube She was given an equal amount of water and salt at one period before the level of the plasma protein fell No edema appeared, and there was no increase in the weight The observations made on this dog are given in detail in the following protocol

Dog 1—This dog was a healthy, well nourished female bull terrier, weighing 169 Kg She was given diet A every day for a period of ninety-eight days, and at no time was plasmapheresis performed The determinations of the total plasma protein, fibrinogen, albumin and globulin were done by the combined methods of Howe,¹⁴ Wu¹⁵ and Koch and McMeekin,¹⁶ as described by Hawk and Bergheim,¹⁷ that for the blood cholesterol as described by Bloor, Pelkan and Allen,¹⁸ that for the blood chloride by the blood method of Whitehorn¹⁹ and that for the blood creatinine by the method of Folin²⁰ determinations were also made with the hematocrit All determinations were made on arterial blood collected in tubes containing 3 mg of sodium oxalate per cubic centimeter of blood drawn The dog was placed in a metabolism cage, and the urine collected over periods of two and three

13 Frisch, R A , Mendel, L B , and Peters, J B The Production of Edema and Serum Protein Deficiency in White Rats by Low Protein Diets, *J Biol Chem* **84** 167, 1929

14 Howe, P E The Determination of Proteins in the Blood, A Micro Method, *J Biol Chem* **49** 109, 1921

15 Wu, Hsien A New Colorimetric Method for the Determination of Plasma Proteins, *J Biol Chem* **51** 33, 1922

16 Koch, F C , and McMeekin, T L A New Direct Nesslerization Micro-Kjeldahl Method and a Modification of the Nessler Folin Reagent for Ammonia, *J Am Chem Soc* **46** 2066, 1924

17 Hawk, P B , and Bergheim, O Practical Physiological Chemistry, ed 9, Philadelphia, P Blakiston's Son & Company, 1926

18 Bloor, W R , Pelkan, K F , and Allen, D M Determination of Fatty Acids (and Cholesterol) in Small Amounts of Blood Plasma, *J Biol Chem* **52** 191, 1922

19 Whitehorn, J C Simplified Method for the Determination of Chlorides in Blood, *J Biol Chem* **45** 449, 1921

20 Folin, O Laboratory Manual of Biologic Chemistry, ed 4, New York, D Appleton & Company, 1927, pp 165 and 243

days was analyzed for chloride and creatinine by the methods of Folin²¹ and for total nitrogen by the method of Folin and Denis²². Fresh specimens of urine were collected frequently for routine clinical analysis. The preliminary control studies gave normal results (table 1).

The dog consumed an average of about 75 per cent of the diet. She lost weight gradually, showing progressive weakness and muscular wasting, but she otherwise remained in good health throughout the experiments, except for a corneal ulcer which developed during the last two weeks. The rectal temperature varied from 101 to 102 F, which is within the normal range for dogs. After she had been on diet A for twenty-eight days, the total plasma protein had dropped from 6.8 to 4.7 Gm per hundred cubic centimeters, and the albumin-globulin ratio had changed from 4.22 to 1.816. The fibrinogen changed from 0.6 to 0.3 Gm per hundred cubic centimeters. At this time, the dog was fed 13.5 Gm of sodium chloride in 1,600 cc of water by stomach tube daily for three days. The solution was isotonic and did not cause diarrhea. The total output of urine for the three days was 4,500 cc, and practically all the chloride was excreted. The output of creatinine was also normal. There was no edema present and no gain in weight.

On the eighty-third day, the total plasma protein had fallen to 3.2 Gm per hundred cubic centimeters, and the albumin-globulin ratio was reversed, 1.317. At this time the same amounts of sodium chloride and water used before (13.5 Gm in 1,600 cc of water) were given daily for three days. Definite pitting edema was noticed at the end of the first day, and at the end of the third day subcutaneous edema was marked. Ascites was easily demonstrable. The dog's weight had increased 1.9 Kg during the three days. About half the chloride was excreted.

Immediately following this period, beginning on the eighty-sixth day, the dog was given 800 cc of water with no added salt for two days. On this regimen she lost weight and the edema decreased, but did not disappear. On the eighty-eighth day, the edema and weight were again increased by the addition of sodium chloride and water. The next day, 1,600 cc of water alone was added, and the animal lost weight. Then for the next two days she was given 11 Gm of potassium chloride in 1,200 cc of water by stomach tube. There was no increase in edema or weight, in fact, she lost 0.8 Kg. Following this period, sodium chloride and water were again administered, and the usual increase in edema and weight occurred.

The cholesterol remained normal except for two determinations on the seventy-seventh and eighty-fourth days, when the readings were 417 and 409, respectively. Both of these readings were controlled by determinations on normal blood. The blood pressure did not vary from the normal. Frequent routine urinalyses showed no abnormalities.

The dog was killed on the ninety-eighth day by the intravenous injection of 10 cc of ether, and autopsy was performed. There was moderate subcutaneous edema, and 600 cc of slightly opalescent fluid was removed from the peritoneal cavity. The specific gravity of this fluid was 1.005, the total protein, 0.17 per cent, and there was 410 mg of chloride per hundred cubic centimeters. The muscles were normal in color and consistency, but were greatly wasted. The left

21 Folin, O. On the Determination of Creatinine and Creatine in Urine, *J Biol Chem* **17** 469, 1914.

22 Folin, O., and Denis, W. Nitrogen Determination by Direct Nesslerization, *J Biol Chem* **26** 486, 1916.

TABLE 1—Results of Studies on Dog 1

Date	Wt	Hem	T P	Alb	Glob	Fib	Chol	BUN	Bl		Cr	Ur	Total Intake of Water, Ce	Total Output of Urine, Ce	Ur Cr	Ur Cl	Ur N	Ur Alb	Edema	Total Intake of Salt	Diet	Comment
									Cr	Cl												
2/28/30	16.9	48.5	6.8	1.0	2.2	0.6	166	8	290				ad lib	850	544	0.15	3.2	0	0		A	Excellent health
3/ 3/30	16.9												ad lib					0	0		A	
3/14/30	16.6												ad lib					0	0		A	
3/18/30	16.1	46.3	5.1	2.7	1.8	0.6	218	8	96				ad lib	650	325	0.24		0	0		A	
3/24/30	16.0	48.0	5.1	2.6	2.5	0.3	276		280	0.6			ad lib					0	0		A	
3/27/30	15.5	47.0	4.7	1.8	2.6	0.3	276		300				1,800	1,500	340	7.83	2.6	0	0	NaCl 39 g	A	No signs of edema
5/ 8/30	13.5												ad lib					0	0		A	
5/11/30	13.3								295	0.6			ad lib	820	195	0.24		0	0		A	
5/22/30	13.1	42.0	3.2	1.3	1.7	0.2	409	6	325	0.6			ad lib					0	0		A	
5/25/30	15.0	33.5	3.6	1.5	1.7	0.4	260	4	340				1,800	2,400	124	3.1	3.1	0	+++	NaCl 39 g	A	Edema marked
5/27/30	13.9												1,600	2,400	198	2.88	2.1	0	+		A	Moderately weak
5/28/30	13.3												ad lib					+	+		A	
5/30/30	13.8												2,400	1,700	187	5.6	2.9	0	+++	NaCl 22 g	A	Edema marked
5/31/30	12.9	30.5	2.9	1.2	1.4	0.2	229		300				ad lib					+	+		A	
6/ 2/30	12.1												2,400	2,400	175	5.7	0.9	0	0	KCl 22 g	A	No edema
6/ 3/30	12.1												ad lib					0	0		A	Weakness, marked muscular wasting
6/ 5/30	13.9	30.0	4.27	1.3	2.4	0.5	240	5	340	0.6			2,400	675	185	1.77	2.1	0	+++	NaCl 22 g	A	Killed (10 cc ether intravenously)

* An interpretation of abbreviations in this and the following tables follows: Wt, weight in kilograms; Hem, hematocrit, percentage of red blood cells; T P, grams of plasma protein per hundred cubic centimeters of blood; Alb, grams of plasma albumin per hundred cubic centimeters of blood; Glob, grams of globulin per hundred cubic centimeters of blood; Fib, grams of fibrinogen per hundred cubic centimeters of blood; Chol, milligrams of cholesterol per hundred cubic centimeters of blood; BUN, milligrams of urea nitrogen per hundred cubic centimeters of blood; Bl Cr, milligrams of creatinine per hundred cubic centimeters of blood; Bl Cl, milligrams of chloride per hundred cubic centimeters of blood; Ur Cr, milligrams of creatinine in urine per twenty-four hours; Ur N, grams of nitrogen in urine per twenty-four hours; and Ur Alb, albumin in urine.

kidney weighed 42 Gm, the right 43 Gm. Grossly, the kidneys appeared normal. The capsules stripped with slight difficulty, leaving a smooth surface. The ratio of the width of the cortex to that of the medulla was normal. The bladder urine showed no albumin, and the sediment showed only an occasional white blood cell. The other organs were normal in weight and appearance.

The microscopic sections were examined by Dr. R. Z. Schulz and Dr. S. B. Wolbach. Microscopic sections of the kidneys, stained with eosin-methylene blue (methylthionine chloride, U.S.P.) and scarlet red, showed a fatty degeneration of the collecting and the distal convoluted tubules and a slight degree in the proximal tubules. This involvement was of moderate degree. The nuclei of the involved tubules were not pyknotic. Occasional loops of Henle contained a few cells with fine fat droplets. A few hyaline casts were present. The glomeruli were of normal appearance, with no evidence of inflammatory cell infiltration, proliferation of the epithelium, fibrosis or deposit of fat either in the intracapsular space or about the capsules. The stroma of the kidney was not increased. Aside from the fatty degeneration, there were no areas suggesting either a healed or an active lesion. The degree of fatty change was more marked than in dog 2.

The liver showed a moderate degree of fatty infiltration which was in both the central and the portal areas, the latter, however, were more extensively involved. The majority of the cells had hypochromatic cytoplasm which was due to fat vacuoles, but in others it was due to the poor staining qualities of the cytoplasm. A considerable number of Kupffer cells filled with a brownish pigment were found in the sinuses. The portal spaces were quite normal in appearance, and there was no fibrosis or infiltration with inflammatory cells.

COMMENT

This animal was the only one used as a control for the diet, so at present we are able to report on only one experiment of this type. Further work will be necessary to establish the fact that such a diet will produce edema in most dogs. Since so much depends on the intake of protein, it may be worth while to emphasize again the fact that this dog ate only three fourths of the diet each day. We believe that this method of producing edema in dogs offers a splendid means for the study of the various problems of this subject.

The microscopic sections of the kidney showed fatty degeneration of the collecting and distal convoluted tubules. These observations are identical with those in the sections from the kidneys of the dogs in which edema was produced by plasmapheresis (see protocols of dogs 2 and 3). There was no evidence of glomerular nephritis in these tissues. The liver also showed fatty infiltration.

There was no evidence of renal insufficiency, the urea nitrogen of the blood remained normal, and there were no urinary abnormalities. The rise in the cholesterol at one period is interesting. This has been observed in dogs that have been starved over a long period of time.²³ We checked the diet for vitamin deficiency, and it was apparently ade-

23 Muller, Gullik Lindh. *The Cholesterol Metabolism in Health and Disease, Medicine* 9:119, 1930.

quate except for vitamin E (antisterility) The corneal ulcer seemed to be traumatic It certainly could not be related to a deficiency in vitamin A, as this vitamin is most abundant in butter and cream

The results of the experiments on the effects of sodium chloride and potassium chloride on the edema of dog 1 are discussed in the next section

THE INFLUENCE OF CERTAIN ELECTROLYTES ON EXPERIMENTAL EDEMA

The importance of the electrolytes in the edema of patients with cardiac and with renal disease was realized by Widal²⁴ (1903), when he advocated a diet with a low content of sodium chloride for the correction of this condition Widal considered the chloride ion as responsible for the retention of the water Blum²⁵ (1909) showed that it is probably the sodium ion that the kidney has difficulty in excreting Blum and his associates²⁶ (1921), Magnus-Levy²⁷ (1920) and Pfeiffer²⁸ (1911) found that edema in patients is increased by the ingestion of sodium chloride, sodium bicarbonate or sodium bromide, but that potassium chloride, ammonium chloride or calcium chloride fails to increase the edema These results strongly suggest that the sodium ion rather than the chloride ion is, of the two, the more important factor in the production of edema

Blackfan and Hamilton²⁹ (1927) demonstrated a low total base in the serum of children suffering with nephrosis Albright and Bauer³⁰ (1929), in their careful study of a patient with nephrosis, made clear the definite relationship between diuresis and the total base excretion in the urine and feces

Van Slyke³¹ (1925) applied the influence of the Donnan equilibrium to the problem of edema The influence of the nondiffusible

24 Widal, F, and Javal, A La cure de dechlororution, Bull et mem Soc med d hôp de Paris **20** 733, 1903

25 Blum, L Ueber die Rolle von Salzen bei der Entstehung von Oedemen, Verhandl d Cong f inn Med **26** 122, 1909

26 Blum, L, Aubel, E, and Hausknecht, R Le mécanisme de l'action du chlorure de potassium dans les néphrites hydropigènes, Compt rend Soc de biol **85** 123, 1921

27 Magnus-Levy, A Alkalichloride und Alkalikarbonate bei Oedemen, Deutsche med Wchnschr **46** 594, 1920

28 Pfeiffer, Emil Wasserretention durch Natriumsalze, Verhandl Cong f inn Med **28** 506, 1911

29 Blackfan, K D, and Hamilton, B Study of the Inorganic Constituents of the Serum in Children with Acute Nephritis, Bull Johns Hopkins Hosp **41** 322, 1927

30 Albright, F, and Bauer, W Acid Base Balance in Nephritis, J Clin Investigation **7** 465, 1929

31 Van Slyke, D D Factors Influencing the Distribution of Electrolytes, Water and Gases in the Animal Body, Philadelphia, J B Lippincott & Company 1926

protein ion in causing an unequal distribution of the diffusible ions (the electrolytes of the plasma) will account for about one fifth of the total osmotic pressure of the plasma when in equilibrium with Ringer's solution. If the plasma proteins are reduced, as in nephrosis, this fraction of the osmotic pressure will also be lowered.

The experimental edema which we produced in dogs is the purest form and the most easily controlled type of edema available for study. There is no evidence of the changes in the permeability of the capillaries or in renal function that one might encounter in a patient with the edema of nephritis, nephrosis or cardiac disease, which could alter the result. Therefore, we believed that it would be of value to study the effects of some of the electrolytes on the edema of our animals.

PROCEDURE

Two healthy female dogs, weighing approximately 17 Kg., were selected. Since all the operations were done on unanesthetized dogs, we selected the animals that were least excitable. We avoided the use of depressing drugs as much as possible, as they often cause vomiting and loss of appetite. The dogs were placed on diet A for a control period of one week. Control studies were carried out as described in the protocol of dog 1.

The apparatus for carrying out plasmapheresis (fig 1) consisted of a Luer-Kaufmann syringe with a no. 18 needle, a 250 cc. pyrex centrifuge bottle and a suction flask with a release pinch cock. The entire apparatus was sterilized for thirty minutes in an Arnold sterilizer. Twenty cubic centimeters of sterile 10 per cent solution of sodium citrate was used for each 250 cc. of blood. The blood was drawn from the femoral artery, as recommended by Barker and Kirk,⁵ directly into the centrifuge bottles. These were centrifuged at 1,800 revolutions a minute for from fifteen to twenty-five minutes; the plasma was removed by suction and was replaced by an equal amount of sterile Ringer's solution, and the suspension was filtered through sterile gauze. This solution was reinjected into a vein under pressure. The procedure was carried out twice a day, 500 cc. of blood being withdrawn each time until the plasma proteins fell to about 3 Gm. per hundred cubic centimeters; daily operations thereafter were sufficient to maintain this low level. We constantly observed a slowly increasing anemia, until the hematocrit reading fell to about 30. It usually remained at about this level. If this procedure was repeated over long periods, the dogs became very weak and refused food. It was then necessary to feed protein to them in the form of milk and meat until they regained strength. This always resulted in a rise in plasma protein, with diuresis and loss of edema. The level of the plasma protein was again lowered by the diet low in protein and plasmapheresis, and the studies were continued. With the plasma proteins at a constant low level, the salts, sodium chloride, sodium bicarbonate and potassium chloride were fed during separate periods.

Dog 2—The dog used in this experiment was a healthy, well nourished, female German shepherd, weighing 16.8 Kg. She was given diet A, which she ate readily. The control studies gave normal results. After a short control period, plasmapheresis was commenced and continued daily for a period of thirty-seven days, with the removal of a minimum of 220 cc. and a maximum of 555 cc. of

plasma daily, making a total of 13,655 cc during this period. Definite pitting edema of the subcutaneous tissue appeared on the eighteenth day. This was not appreciably increased during a two day period when the intake of water was increased to 1,600 cc daily. No sodium chloride had been added at the time the edema appeared. On the twenty-first day, the dog was placed on a three day metabolism experiment, receiving 13.9 Gm of sodium chloride in 1,600 cc of water by stomach tube daily. The subcutaneous edema increased markedly, ascites appeared, and the dog gained 3 Kg in weight (table 2). This regimen was repeated for two more days, and the weight increased 2.4 Kg. During the next three days, she was given 1,600 cc of water alone daily, there was little change in the weight during this period. On the twenty-ninth day, she was started on

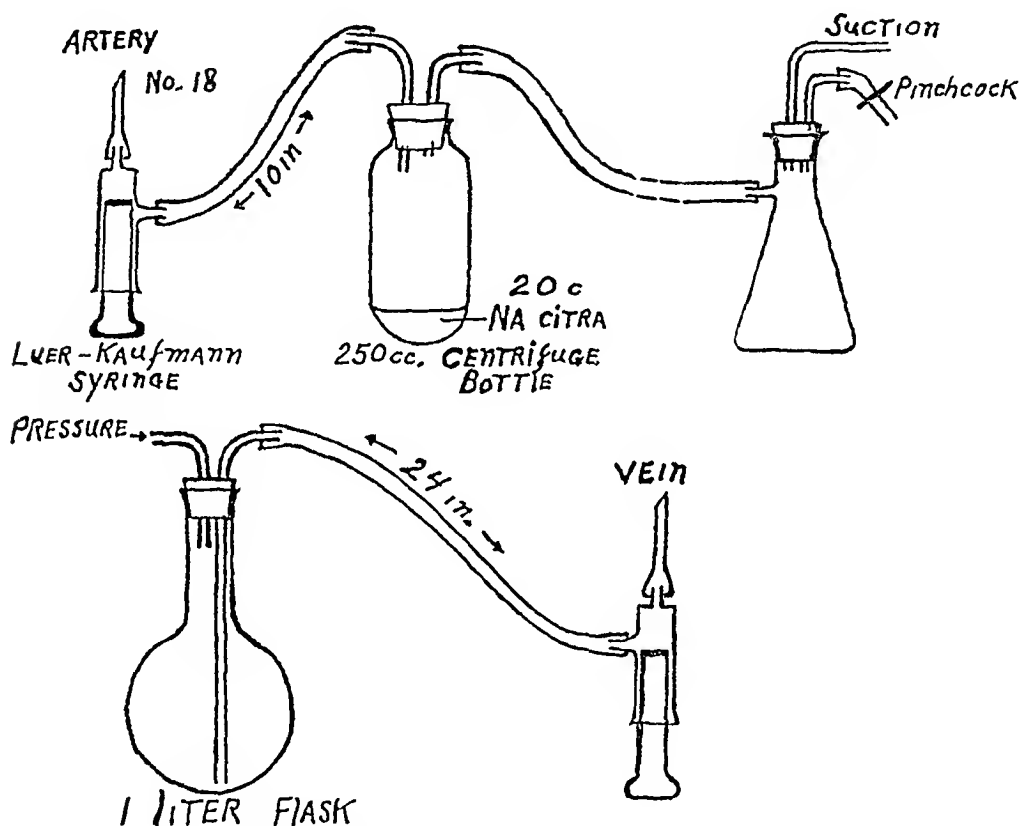


Fig 1—Apparatus for plasmapheresis

a four day metabolism experiment during which she received 19 Gm of sodium bicarbonate in 1,600 cc of water daily. She gained 0.3 Kg during the first day, but from that time on she lost weight. Diuresis set in, and the edema decreased markedly, this continued through the next two days when no bicarbonate was given, and even persisted through a period of three days when 13 Gm of sodium chloride in 1,600 cc of water was administered daily. At this time, because of the low hematocrit reading, it was necessary to give the dog a transfusion with 500 cc of blood from a normal dog. She had become weak and refused diet A, so she was allowed to convalesce for ten days on a diet high in protein.

The second period of plasmapheresis was then commenced and was continued during sixteen days, and a total of 5,810 cc of plasma was removed. Edema was noticed this time on the seventh day. The amount of edema or the weight failed to increase with the administration of large amounts of water alone. However, when sodium chloride was added, the usual increase in edema and weight was

TABLE 2—Results of Studies on Dog 2

Date, 1930	Wt	B P	Hem	T P	Alb	Glob	Erb	Chol	B U N	B U Cr	B I Cr	B I Cl	Duration of Metabolism Intake of Water, Ce	Total Output of Urine, Ce	Ur Cr	Ur Cr	Ur N	Ur Alb	Edema	Total Intake of Salt†	Diet	Plasma Carbon Dioxide, per Cent Plasma	Total Amount of Re moved, Ce	Comment
2/24 16.8			51.3	5.5	3.1	2.2	0.2	231	7	2.0	270	270	ad lib	1,750	137	0.43	1.7	0	0		A	0	0	Control period
2/26 16.1	107		46.6					271			280	280	ad lib					0	0		A	4,710	0	
3/11 15.2											310	310	ad lib	2,500	220	0.4	2.1	0	0	0	A	5,915	0	
3/11 15.0			32.2	2.5	1.2	1.2	0.1	171					ad lib					0	0	+	A	6,730	0	
3/16 15.2	105		31.1	2.5	1.2	1.2	0.1	135	8	0.6	310	310	ad lib	2,800	338	0.9	2.2	0	0	+	A	7,730	0	
3/18 15.2													ad lib					0	0	+	A	8,280	0	
3/19 15.2											330	330	ad lib	1,300	217	1.58		0	0	+	A	9,305	0	
3/22 18.2	100		35.5	2.4	1.0	1.2	0.2	151	5				ad lib	450	225	1.05	1.9	0	0	+	A	9,915	0	
3/24 20.6	110		32.1	2.5	1.1	1.2	0.2	136	0.5	0.5	325	325	ad lib	2,750	295	2.21	0.7	0	0	+	A	10,840	0	Weakness marked
3/27 20.5			25.1	2.5	1.0	1.2	0.3	147					ad lib	6,400	3,600	2.18	2.9	0	0	+	A	12,115	0	
3/31 20.4			27.1	2.6	1.2	1.1	0.3	152			307	307	ad lib	3,800	3,800	3.15	4.0	0	0	+	A	12,775	0	
4/2 17.1			21.7	3.0	0.9	1.8	0.3	189	0.6	0.6	330	330	ad lib	3,200	3,200	3.31		0	0	+	A	13,655	0	Poor condition, muscular wasting marked
4/5* 16.1	110		36.0†	2.8	0.9	1.9	0.13		5		273	273	ad lib	1,100	273	6.83		0	0	+	A		0	
4/16† 14.7			34.7	5.0	2.7	2.5	0.4	142	0.9	0.9	320	320	ad lib					0	0	0	A	1,170	0	Condition much improved
4/20 14.3													ad lib					0	0	0	A	2,280	0	
4/22 14.5			31.5	3.0	1.3	1.5	0.2				40	40	ad lib	900	209	0.56	1.4	0	0	0	A	2,735	0	
4/23 14.5											21	21	ad lib	1,500		0.75	2.7	0	0	+	A	3,275	0	
4/24 14.4			20.4	2.85	1.36	1.35	0.17		0.6		290	290	ad lib					0	0	+	A	4,010	0	
4/26 17.1													ad lib	350	248	1.2	1.7	0	0	+	A	4,285	0	
4/27 17.5			31.0	2.6	1.1	1.4	0.1				50	50	ad lib	900	297	1.12	2.1	0	0	+	A	4,780	0	
4/28 18.2											20	20	ad lib	600	211	0.66	1.8	0	0	+	A	5,185	0	
4/29 18.6			34.9	2.9	1.1	1.6	0.2	169					ad lib	700	259	0.55	1.9	0	0	+	A	5,485	0	
4/30 18.0											21	21	ad lib	1,020		0.81	2.6	0	0	+	A	5,485	0	
5/1 18.3			33.8	2.5	0.9	1.1	0.24		0.6	0.6	295	295	ad lib	1,600	200	1.15	1.1	0	0	+	A	5,485	0	
5/2 18.8											21	21	ad lib	1,600				0	0	+	A	5,485	0	
5/2 18.8	110		34.0	3.7	1.5	1.8	0.4						ad lib	600				0	0	+	A	5,810	0	
5/7# 12.5													ad lib					0	0	0	A	1,360	0	
5/11 12.6			34.5	2.5	1.0	1.3	0.2				310	310	ad lib	850	181	0.46	1.15	0	0	+	A	2,190	0	
5/13 12.9			36.2	2.9	1.1	1.6	0.2						ad lib	1,600	213	1.6	2.7	0	0	+	A	2,435	0	
5/14 12.7	90		33.0	2.7	1.0	1.3	0.1	180	0.6		290	290	ad lib	3,200	192	6.8	1.7	0	0	+	A	3,300	0	
5/16 12.5													ad lib					0	0	+	A	3,515	0	
5/17 12.45													ad lib	730		1.78	1.5	0	0	+	A	4,195	0	
5/19 15.9			32.0	2.2	0.9	1.0	0.2				315	315	ad lib	1,550	215	0.62	1.5	0	0	+	A	4,855	0	
5/21 15.1	110		30.5	2.5	0.9	1.4	0.2				317	317	ad lib	2,100	181	2.88	1.5	0	0	+	A	5,460	0	
5/23 11.7			29.7	2.5	1.0	1.3	0.2	183	7	0.6	325	325	ad lib					0	0	+	A	5,790	0	
5/24 15.5	100		30.2								325	325	ad lib					0	0	+	A		0	Killed while it had edema (10 cc of ether intravenously)

* The sudden rise in the hematocrit was due to the addition of blood cells from 500 cc of normal dog blood on the fourth

† The intake of chloride varied from 0.2 to 0.9 Gm daily except as indicated in this column

‡ A diet high in protein (consisting of diet A plus 600 Gm of meat and 500 cc of milk) was given from the sixth to the sixteenth, inclusively

§ Diet A, see protocol of dog 1

A diet of protein (consisting of diet A plus 200 cc of milk) was given from the third to the seventh, inclusively

observed (fig 2) After this period she was given 19 Gm of sodium bicarbonate in 1,600 cc of water daily for three days At this time there was a definite increase in edema and a gain in weight of 11 Kg (fig 2 and table 2) A further increase of 0.5 Kg in weight occurred with the administration of 13.5 Gm of sodium chloride in 1,600 cc of water She was then allowed another short period of convalescence on a diet moderately high in protein (table 2)

The third period of plasmapheresis was then started and continued for eighteen days, and a total of 5,790 cc of plasma was removed. Edema was noticed on the sixth day. The dog was then given 13.5 Gm of potassium chloride in 2,200 cc of water daily for two days. There was no gain in weight and no increase in edema, however, after the administration of 10 Gm of sodium chloride in 1,200 cc of water daily for the next two days there was a prompt rise in weight, and

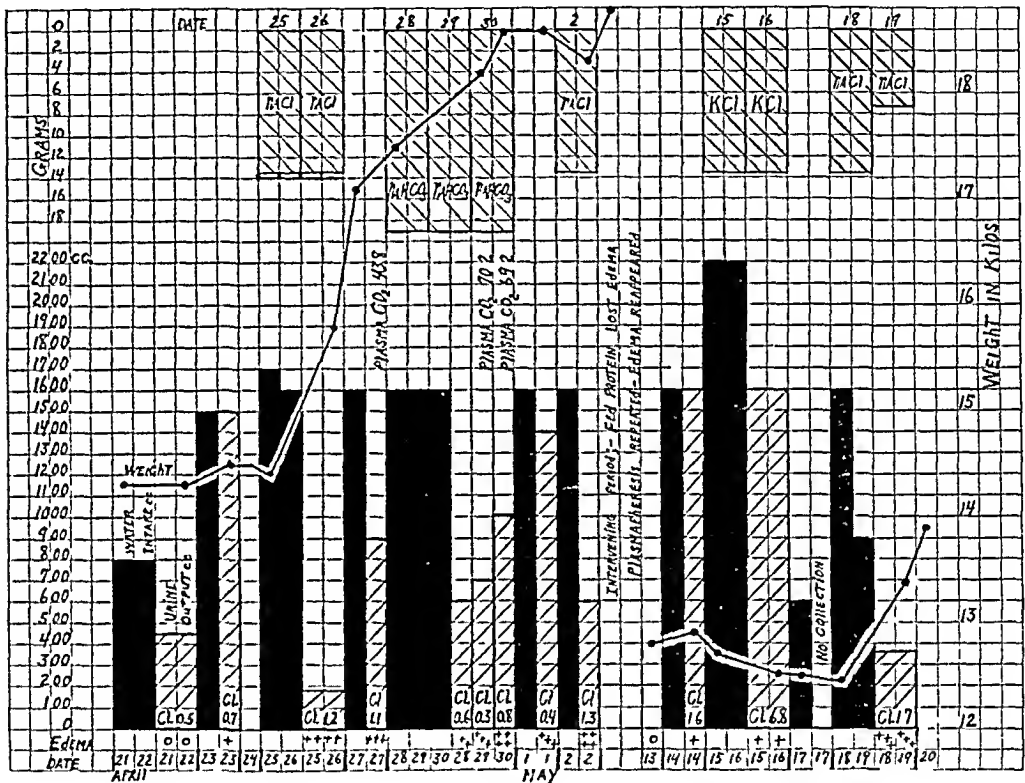


Fig 2—Graphic representation of experiments on dog 2. Determinations on the intake and output of fluid are blocked in at the base and those on the salt added to the diet at the top of the chart.

the edema was considerably increased (fig 2 and table 2) After two days with no added salt in the diet, we attempted to feed her 5 cc of concentrated hydrochloric acid in 800 cc of water twice daily for two days The dog vomited an unknown amount of this acid solution, so quantitative observations were inaccurate however, a sufficient amount was retained to lower the carbon dioxide-combining power of the plasma from 41 to 35 per cent There was a slight decrease in edema and she lost 0.4 Kg Sodium chloride administered during the next day brought about an increase of 0.8 Kg in weight

The blood chloride showed little variation during the entire period. The creatinine index remained normal. There were no albumin or casts in the urine at any time. The rectal temperature varied from 101 to 103 F. The systolic blood pressure ranged from 95 to 110 mm. of mercury.

On the ninety-seventh day, while the dog had edema, it was killed by the intravenous injection of 10 cc of ether, and autopsy was performed. There was marked edema of the subcutaneous tissue, and 1,500 cc of fluid was removed from the peritoneal cavity. The specific gravity of this fluid was 1.006. The muscles were normal in color and consistency, but were greatly wasted. The left kidney weighed 39 Gm, the right, 41 Gm. The capsules stripped easily, leaving a smooth glistening surface which contained many small white flecks but no scars. The ratio of the width of the cortex to the medulla was normal. The urine from the bladder showed no albumin, and the sediment showed only an occasional white blood cell. The other organs were normal in appearance and weight.

The sections of the kidney stained with eosin-methylene blue and scarlet red showed a fatty degeneration of the collecting tubules, of the distal convoluted tubules and to a very slight extent of the proximal convoluted tubules. In many instances the fat was at the base of the cell and about the nucleus, and at times it filled the entire cell. The nuclei were well preserved and a hyperchromatic or pyknotic nucleus was rarely seen. The remainder of the kidney cells showed only edema. The loops of Henle and the proximal convoluted tubules on the whole were well preserved. The tubules contained only an occasional hyaline cast. The glomeruli showed no lesions in the form of a fibrosis, epithelial proliferation or infiltration with inflammatory cells. There was no increase in the interstitial tissue.

Dog 3—Dog 3 was a well nourished, healthy, female shepherd dog, weighing 17.1 Kg. This dog was given diet A during the periods of plasmapheresis and usually consumed all of it. All of the control studies were normal (table 3). The first period of plasmapheresis was then commenced and continued for twenty-two days, with the removal of from 195 to 515 cc of plasma daily, making a total of 7,095 cc. Edema was first noticed on the seventeenth day. A three day metabolism experiment with the addition of 1,600 cc of water daily by stomach tube failed to increase the edema or the weight. However, during the next two days, 13.5 Gm of sodium chloride was added with the same amount of water each day, the edema increased markedly, and there was a gain in weight of 1.9 Kg. An attempt to give the dog sodium bicarbonate failed because of increasing weakness and loss of appetite. At this time plasmapheresis was discontinued and she was placed on a diet high in protein for three days, she regained her usual good health.

The second period of plasmapheresis was started and continued for twelve days, with a total removal of 5,200 cc of plasma. Edema was first noticed on the seventh day. The dog again gained in weight and edema on sodium chloride given as before, and she maintained the same condition when given water alone for one day.

The dog was then placed on a three day experiment, receiving 19 Gm of sodium bicarbonate in 1,600 cc of water daily. This time she did not become ill, and there was a gain in weight of 0.9 Kg, with a definite increase in edema. During the experiment with sodium bicarbonate the dog was given a transfusion of blood because of the accidental clotting of her own blood during the centrifugation. This transfusion was performed with the blood cells from 500 cc of normal dog's blood suspended in saline. The experiment was followed with 1,600 cc of water, and this resulted in a further increase in edema and a gain of 0.2 Kg. This concluded the second period of plasmapheresis. Because of the dog's increasing weakness, 200 cc of milk was added to diet A for six days.

The third period was then commenced and continued for fourteen days with a total removal of 4,605 cc of plasma. Edema appeared on the seventh day. Again

TABLE 3—Results of Studies on Dog 3

Date	Wt	Hem	T.P.	Alb	Glob	Fib	Chol	B.U. N	B.U. Cr	B.U. Cl	Total Metab Output of H ₂ O	Total Intake of Urine, Ce	Ur Cr	Ur Cl	Ur N	Ur Alb	Edema	Total Intake of Salt*	Diet	Total Amount of Plasma Re- moved, Ce	Comment																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																							

* The intake of chloride varied from 0.2 to 0.9 Gm daily, except as indicated in the column headed "total intake of salt." This was due to the excess of chloride in the Ringer's solution over the average plasma chloride.

† A diet of protein (consisting of diet A plus 600 Gm of meat and 500 cc of milk) was given from the eighteenth to the twentieth, inclusively.

‡ The rise in the hematocrit was due to the addition of blood cells from 500 cc of normal dog blood.

§ A diet of protein (consisting of diet A plus 200 cc of milk) was given from the third to the eighth, inclusively.

the dog failed to gain weight or the edema to increase during a one day experiment with 2,200 cc of water. This was followed by a two day experiment, during which we administered 13.5 Gm of potassium chloride in 2,200 cc of water daily. There was no increase in edema or in weight, in fact, there was a loss of 0.6 Kg. The next day 1,600 cc of water alone was given, and there was no change in weight, but an experiment on the following two days, consisting of a daily intake of 10.3 Gm of sodium chloride in 1,300 cc of water, caused a marked increase in edema and a gain of 1.5 Kg. We attempted to administer dilute hydrochloric acid, but this dog vomited all of the solution. We felt that it might be interesting to kill one dog while she had massive edema and the other when there was no edema, in order to see if there was any detectable change in the fixed tissue. Therefore, dog 3 was given a diet high in protein, the edema disappeared, and she was killed on the ninetyeth day of the experiment by the intravenous injection of 10 cc of ether. Frequent urinalyses during the experimental period and urinalysis at autopsy revealed no albumin or casts. These results were substantiated by the failure to find casts in the renal tubules (see autopsy). The creatinine index remained normal throughout. The rectal temperatures showed no variation from the normal.

No subcutaneous edema or excess of fluid in the cavities of the body were found at autopsy. The left kidney weighed 62.5 Gm, and the right, 62 Gm. The capsules stripped readily, leaving a smooth, glistening surface with no gross abnormality. The urine of the bladder showed no albumin, and the sediment contained only an occasional white blood cell. All of the other organs were normal in appearance and weight.

The sections of the kidney stained with eosin-methylene blue and scarlet red revealed a rather marked fatty degeneration of the collecting and distal convoluted tubules, characterized by vacuoles of fat of varying sizes, which at times completely filled the cells and caused some enlargement of the cell, so that the lumen of the tubule was narrowed. The degree of involvement in this kidney was greater than that in dog 2 and more nearly approached the degree in involvement found in dog 1. It differed from the latter, however, in that the fat was limited to the distal and convoluted tubules with almost no fat in the proximal convoluted tubules or in the loops of Henle. The glomeruli were normal in appearance, there was no proliferation of the capsule or tuft epithelium, fibrosis or infiltration with inflammatory cells. There was no hyaline membrane with fat contained around the glomeruli. There was no increase in the interstitial tissue, and the occasional area of lymphocytic infiltration was so small that it was hardly worth consideration.

RESULTS AND COMMENT

The Influence of Sodium Chloride on Experimental Edema—In the dogs edema did not develop until the plasma proteins fell to about 3 Gm and the albumin to about 1 Gm per hundred cubic centimeters. At this level, without the use of excessive amounts of water or sodium chloride, dogs 2 and 3 showed definite pitting edema. The use of large amounts of distilled water (1,600 cc) by stomach tube did not increase the edema or the weight appreciably, but when 13 Gm of sodium chloride per day was added to the water massive edema appeared, accompanied by a rapid increase in weight. There were ascites and marked pitting edema of the skin, especially where there were loose folds of flesh and particularly in the hind legs. It seems that, given

a low plasma protein, the amount of edema is determined by the amount of sodium chloride administered. This is demonstrated in figure 2. We wish to make clear that a constant low level of plasma proteins was maintained while the influence of the various salts was studied.

The Influence of Sodium Bicarbonate on Experimental Edema—We have not included in the following discussion the results of the first experiment with sodium bicarbonate, which is described in the protocol of dog 2, for reasons given in section 2 of the next division of the paper.

The administration of sodium bicarbonate gave the same sort of response as did sodium chloride but to a lesser degree, in spite of the use of larger amounts of the bicarbonate, i. e., 19 Gm per day. The amount used was sufficient to change the plasma carbon dioxide-combining power from 44 to 70 per cent in dog 2, and from 49 to 69 per cent in dog 3, during the first twenty-four hours. During the three days that this salt was given, the weight of dog 2 increased 1.1 Kg, and the weight of dog 3 increased 1 Kg (fig. 2 and tables 2 and 3). We were unable to continue giving sodium bicarbonate to these dogs, as they were very weak and refused food. This result is interesting in view of the enthusiasm for the use of alkali as a diuretic which has been renewed recently by Osman³² and also by Bennett³³. However, it is worthy of note that half of the alkaline salts given by these authors were potassium salts. After our experiment was concluded the dogs were given meat and milk, the edema promptly disappeared, and they regained their strength.

The Influence of Potassium Chloride on Experimental Edema—After the level of the plasma protein was lowered by plasmapheresis and slight edema was established in both dogs, 13.5 Gm of potassium chloride was administered daily for two days. This was given in water sufficient to make a nearly isotonic solution (1,600 cc). During this two day period dog 2, instead of gaining weight, lost 0.2 Kg, and dog 3 lost 0.6 Kg (fig. 2 and tables 2 and 3). In order to ascertain whether or not this loss of weight was due to the onset of a spontaneous diuresis, we administered sodium chloride, and both dogs showed a typical rise in weight, and the edema was increased. This failure to increase edema with the administration of potassium chloride was also observed with dog 1.

The Influence of Hydrochloric Acid on Experimental Edema—The administration of a dilute solution of hydrochloric acid to these dogs induced vomiting, so we were unable to make quantitative obser-

32 Osman, A. A. Studies in Bright's Disease, Guy's Hosp. Rep. **77** 386, 1927.

33 Bennett, T. I. Nephritis. Its Problems and Treatment, London, Oxford University Press, 1929.

vations. However, a sufficient amount was retained by dog 2 to lower the carbon dioxide-combining power of the plasma from 41 to 35 per cent, and this was accompanied by a loss of 0.2 Kg.

The output of creatinine was studied as a check on the collection of urine and as an index of renal function. There was a gradual fall in both the creatinine of the blood and that of the urine, so that the index $\frac{\text{urine creatinine}}{\text{blood creatinine}}$ showed no fall. The chloride metabolism was studied. We believe that a study of the total base or the sodium metabolism would be of more value than one of the chloride, but we felt that in these preliminary experiments it would be better to overcome some of the technical difficulties accompanying the production of edema before attacking the problem of total base determinations in the serum, urine and feces of dogs. We regret that the number of experiments reported here is necessarily small, but we have tried to avoid drawing conclusions that are too broad, except when our conclusions were strengthened by previous good experimentation of others.

OTHER INTERESTING PHASES OF EDEMA

1 *Relation of Edema to the Chloride Excreting Power of the Kidney*—In the past many workers expressed the belief that the rôle of sodium chloride in the production of edema is due to the failure of the kidney to excrete either the sodium or the chloride ion. The result of this is a retention of salt in the tissues of the body, this salt holds water with it, hence there is edema. However, at present most of the investigators who are interested in the problems of edema believe that the kidney has little to do with the retention of salt, particularly in the edemas originating in low plasma protein. It is more likely that the lowered osmotic pressure of the plasma proteins allows fluid to escape into the tissues, and this fluid carries salt with it which is retained there, so that the kidney is never offered the major portion of the salt for excretion. We have evidence that during the edematous periods, the kidneys of our dogs were capable of excreting chloride normally. Unfortunately we are unable to offer the same evidence for the sodium ion as the excretion of sodium was not studied.

The function of the kidneys of our dogs was normal by the usual methods of study. The intake of chloride, except during the periods when measured amounts were added, ranged from 0.2 to 0.8 Gm. per day. The output of chloride was roughly equal to the intake even during the periods of massive edema unless the weight was increasing. If the dogs were gaining weight, the output of chloride would obviously be less than the intake, because the chloride would be retained in the tissues along with the base. Even while the dogs were rapidly gaining weight and edema was increasing as a result of feeding large amounts of sodium chloride, the kidneys were excreting much more chloride than they

normally excreted. For example, dog 2 was given a total of 19.6 Gm of chloride (36 Gm of sodium chloride) during three days while the plasma proteins were low, and she excreted 4.7 Gm of chloride. During this period she gained 3 Kg. When the plasma proteins were higher, she was given the same amount of chloride and excreted all of it in the three days (table 1). The same result was observed in dog 3. All of the chloride was also excreted when potassium chloride was given. This ability to excrete large amounts of chloride during the edematous period is certainly evidence against any defect in the chloride excreting power of the kidney.

2 *Spontaneous Diuresis in the Edema of Low Plasma Proteins*—

There has been a hesitancy to accept low plasma proteins as the main factor in the causation of this type of edema, because certain patients who have low plasma proteins have no edema, also during the course of observation of patients with nephrosis who show edema, one will at times observe a spontaneous diuresis with the loss of edema in spite of persistence of low plasma proteins and no change in the albumin-globulin ratio. Moore and Van Slyke⁹ reported such a case and called attention to some "unknown factor" which may cause this. Leiter,⁴ as well as Baiker and Kirk,⁵ observed a tendency for the edema in their dogs to disappear as the experiments were prolonged, in spite of the maintenance of low levels of plasma protein.

This type of spontaneous diuresis probably occurred in one of our dogs (dog 2) while we were administering sodium bicarbonate, and was the cause of some confusion. This dog had had extensive edema for fifteen days when we gave her 19 Gm of sodium bicarbonate daily during four days. She gained 0.3 Kg the first day and then began to lose weight rapidly, the edema decreased, and there was a marked diuresis. We then gave her 13.5 Gm of sodium chloride daily for three days, which in every other experiment resulted in a rapid rise in weight, but at this time the diuresis persisted and the edema practically disappeared. A chemical analysis of the blood revealed no cause for this, the total plasma proteins were 2.8 Gm and the albumin 0.9 Gm per hundred cubic centimeters. The carbon dioxide had fallen to the original level of 39 per cent, and the results of other studies were normal. When the same amount of sodium bicarbonate was given to this dog after it had been edematous for only a short period, she gained weight in the same way in which dog 3 did. Jansen,³⁴ Magnus-Levy²⁷ and others always observed an increase in the edema of their patients after the administration of sodium bicarbonate. For these reasons we believe that a spontaneous diuresis occurred during this period of study, and that probably the sodium bicarbonate had little

³⁴ Jansen, W. H. Der Oedemkrankheit, *Deutsches Arch f klin Med* **131** 144, 1919.

or nothing to do with it. The onset of such a spontaneous diuresis during the study of diuretic drugs may be the cause of considerable confusion and may be a reason for false ideas concerning their efficacy.

3 *Relation of Experimental Edema Produced by Lowering the Plasma Proteins to Nephrosis*—Barker and Kirk drew attention to the similarity between the edema of dogs produced through plasmapheresis and the clinical syndrome of nephrosis. We have been able to confirm their observations. However, we were not able to find glomerular lesions or albumin or casts in the urine, but we invariably found an excessive amount of lipid deposit in the renal tubules. In order to control this side of our problem, we made fat stains from the fresh kidney tissue of two dogs, one young and the other full grown. Both showed a few fat droplets in the renal tubules, but the amount present was not comparable to that found in our experimental animals. Glomerular lesions of various sorts were not uncommon in these so-called normal dogs.

The picture in the dog with edema produced through deprivation of protein was identical with that in the dogs in which edema had been produced by plasmapheresis. We feel that this condition is not nephrosis in the dog, but we regard the syndrome observed in all of these dogs as a specific result of the deprivation of protein. We may go even further and state that perhaps certain changes in patients with nephrosis, namely, edema, low plasma protein with reversed albumin-globulin ratio, fatty degeneration of the renal tubules, low basal metabolic rate and possibly cholesterolemia, is the result of deprivation of protein, which in this instance is the result of loss of protein through the kidney, often augmented by a diet low in protein.

4 *The Reasons for the Reversal of the Albumin-Globulin Ratio*—It has been suggested that the reversal in the albumin-globulin ratio in nephrosis in human beings is due to the selective loss of the smaller albumin molecule through the kidney.³⁵ As early as 1916, Kerr, Hurwitz and Whipple³⁶ observed a reversal in the albumin-globulin ratio in their excellent studies on plasmapheresis, in such experiments, there is no selective loss of albumin. They gave three possible reasons for this phenomenon, namely, the fact that shock or infection occurred, that globulin is regenerated faster than albumin in serum, or that during the forced regeneration the precipitation values of the proteins may vary from normal. We can eliminate the first possibility, for there was neither shock nor infection in any of our animals. We were unable to find any work which showed that the precipitation factors of the protein

35 Cowie, D. M., Jarvis, K. M., and Cooperstock, M. Metabolism Studies in Nephrosis, *Am J Dis Child* **40** 465 (Sept.) 1930.

36 Kerr, W. J., Hurwitz, S. H., and Whipple, G. H. Regeneration of Blood Serum Proteins, *Am J Physiol* **47** 356, 1918.

were changed. Probably the simplest explanation is that the body is able to regenerate globulin from the tissues more readily under these conditions than it does albumin.

5 *The Edema Fluid in Experimental Edema*—The edema fluid was studied in dog 1, in which edema was produced by a diet, and in dog 2, in which edema was produced by diet and plasmapheresis (table 4). The figures for protein and chloride are essentially the same for the two dogs. The protein is a little higher than is usual in this type of edema fluid, possibly because of contamination with small traces of blood during collection. The figure for chloride agrees with that found in the edema fluid from patients with nephrosis and in normal spinal fluid. It is interesting to note that during the period of administration of sodium bicarbonate, the level of chloride of the edema fluid fell from 450 to 375 mg per hundred cubic centimeters.

TABLE 4—*Summary of Determinations Made on Edema Fluid*

Dog	Date	T P of Edema Fluid, per Cent	Cl of Edema Fluid, Mg per 100 Cc
1	6/ 6/30	0.21	420
2	3/22/30	0.19	420
	3/25/30	0.19	450
	3/29/30*	0.13	375

* Determinations on this date were made after the administration of sodium bicarbonate.

CONCLUSION

1 Edema was produced in a dog by a diet low in protein but adequate in carbohydrate and fat. The chemical, pathologic and clinical observations made on this animal were essentially the same as the observations made on those in which edema had been produced by selective removal of plasma proteins (plasmapheresis).

2 The chemical, pathologic and clinical determination made on all of the dogs were similar to those found for dogs in which edema was produced through an inadequacy of protein in the diet.

3 Sodium chloride and sodium bicarbonate increased the edema of dogs with a constant low level of plasma protein, while potassium chloride did not. This is further evidence that the sodium ion has a greater influence on edema than the chloride ion. It seems probable that given a low plasma protein, the amount of edema is determined by the quantity of the intake of the sodium ion.

4 Evidence is presented to show that the power of the kidney for excreting chloride is normal in edema produced experimentally with a low plasma protein.

Dr J. P. O'Hare supervised us in this work and Miss Margaret Driscoll gave technical aid.

INSULIN

SOME EFFECTS ON NORMAL RABBITS PROTECTED FROM
HYPOGLYCEMIA BY INGESTION OF DEXTROSE *

ROBERT F LOEB, M D

EMILY GUILD NICHOLS

AND

BERYL H PAIGE

NEW YORK

In many clinics, the technic of insulin therapy as applied to the treatment for diabetic acidosis has undergone a series of changes since the introduction of insulin in 1922. At the Presbyterian Hospital, as elsewhere, brilliant therapeutic results were obtained in the early days of the use of insulin by the administration of relatively small doses of the hormone in conjunction with the supportive measures employed in the pre-insulin era. When large quantities of insulin became available for clinical use, massive doses were employed on the assumption that they would bring about more rapid alleviation of the ketosis by augmenting the oxidation of dextrose. The results of this type of therapy were, however, frankly disappointing, in part at least, because too much emphasis was placed on disturbances of carbohydrate oxidation and not enough on the significant consequences of severe ketosis, namely, loss of fixed base, dehydration and collapse. In recent years, patients in this clinic have again been treated with small doses of insulin, more attention has been paid to the dangers of dehydration, and the results have again been most gratifying.

In spite of this improvement in the methods of treatment for diabetic acidosis, a number of patients die, and death not infrequently occurs some hours after the diabetes and ketosis have been controlled. The cause of the fatal outcome in these cases has frequently been ascribed to a deleterious effect of insulin. This idea has led to numerous clinical and laboratory studies to determine possible toxic effects of insulin on

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* From the Departments of Medicine and Pathology of the College of Physicians and Surgeons of Columbia University and the Presbyterian Hospital

the heart, circulation, nervous system, muscles and suprarenal glands¹ Most of these investigations have been concerned with effects of the hormone in the presence of severe hypoglycemia In view of the fact that this state is rarely encountered in the treatment for diabetic acidosis, it seemed desirable to study the comparative effects of small and massive doses of commercial and of crystalline insulin in the normal animal, protected against hypoglycemic shock by means of adequate amounts of dextrose

In this work an attempt has been made (1) to determine the possible general toxic effects of large doses of insulin in contrast to small ones, (2) to compare the actual, as well as the relative, effects of small and large doses of the hormone on the hyperglycemia resulting from continuous absorption of dextrose, (3) to observe the effects on the glycogen storage in the liver, and (4) to note any possible histologic changes produced in the adrenal glands and liver It was hoped that such a study might furnish evidence that might be of value in determining the relative merits of small and of massive doses of insulin

EXPERIMENTAL WORK

Two main groups of studies were made on healthy adult rabbits One group of animals was fed on a diet of oats and cabbage up to the time of the experiment, to insure the presence of large stores of glycogen A second group was deprived of food for forty-eight hours, so that the content of glycogen at the beginning of the experiment might be at a minimum

After initial determinations of blood sugar, the animals were given 12 Gm of dextrose (in 50 per cent solution) per kilogram of body weight by means of a stomach tube The feedings of dextrose were immediately followed by intravenous injections of insulin, and samples of blood for sugar determinations were taken at hourly intervals for a period of four hours At the end of this time a second and equal dose of dextrose was given, again followed by insulin, and the blood sugar was determined for the next three hours at hourly intervals Seven and one-half hours after the initial dextrose feeding, the animals were killed by a sudden blow, and parts of the liver were immediately removed for determinations of glycogen

In each group of animals, one series received no insulin, another received 7 clinical units of insulin per kilogram (i e, "small" doses) and a third series received 75 units of insulin per kilogram (i e, "massive" doses) Crystalline insulin was prepared from commercial insulin furnished us by the E R Squibb Company The preparation of the crystals was carried on according to the method

1 Edwards, D J, and Page, I H *Am J Physiol* **69** 177, 1924 Hornung, S *Compt rend Soc de biol* **97** 1500, 1927 Labbé, M, and Boulon, R *Médecine* **9** 746, 1928 Sundberg, C G *Compt rend Soc de biol* **89** 807, 1923 Jung, L, and Auger, L *Compt rend Soc de biol* **101** 821, 1929 Raiha, C E *Skandinav Arch f Physiol* **56** 243, 1929 Baur, H *Beitr z path Anat u z allg Path* **83** 1, 1929 Hetenyi, G *Wien Arch f inn Med* **13** 95, 1926 Reinwein, H *Deutsche med Wchnschr* **55** 951, 1929 Doisy, E A, and Weber, C J *J Biol Chem* **58** 721, 1924

of Prof John Abel, who furnished us with sample crystals. The crystals obtained by us were identical with those described by Abel, and they assayed about 25 units per milligram.

Blood sugar was determined by the method of Hagedorn and Jensen² on samples obtained from the central artery of the ear. Determinations of glycogen were made according to a modification of the Pfluger method, and no estimation was made of reducing substances other than dextrose as the quantities of glycogen were, in most cases, large enough to eliminate great errors from this source. Only the comparative values for glycogen in various groups of animals seemed of interest. All analytic procedures were carried out in duplicate.

Animals in which any appreciable diarrhea occurred during the experiment were discarded. Loss of insulin through renal excretion was slight, as most of the animals voided but little. Furthermore, in one instance, 20 per cent of the urine excreted by a rabbit in seven hours after receiving 444 units of insulin intravenously was injected subcutaneously into a second rabbit and failed to cause convulsions in nine hours.

For the histologic studies, both adrenal glands and the liver were removed as soon as possible after death. The organs were weighed, as were the animals after the removal of the stomach and intestinal tract. Comparisons of the weights of the adrenals and liver in relation to body weight were noted in the various groups of experiments performed. The adrenal glands were sectioned, part being placed in "Muller-formol" and the remainder in a formaldehyde solution (solution of formaldehyde, U S P 1, water to make 10). Blocks of tissue fixed in "Muller-formol" were transferred to Muller's solution, washed in running water, dehydrated in alcohol and embedded in paraffin, and several sets of serial sections were stained with hematoxylin and eosin. Frozen sections from the tissue fixed in formaldehyde were stained with scharlach R. Since a comparison of the sections of the adrenal glands of well-fed and of starved control animals to which no insulin was administered showed great variation in the widths of the cortex and of the medulla in individual animals, no accurate measurements were made, the widths of layers as seen in the hematoxylin-eosin preparation being merely compared and recorded as "wide," "average" and "narrow." From the hematoxylin-eosin sections the intensity of the chromaffin staining was also determined, and a search was made for any structural changes that might be present. From the frozen section stained with scharlach R the relative amounts of lipid in the different glands were determined.

Blocks of liver tissue were fixed in Zenker's solution, 10 per cent formaldehyde and 95 per cent alcohol. From the blocks fixed in Zenker's solution paraffin sections were obtained and stained with hematoxylin and eosin. Tissue fixed in formaldehyde was used for frozen sections which were stained with scharlach R. From the blocks fixed in alcohol, celloidin sections were stained with Best's carmine to demonstrate glycogen.

RESULTS

Blood Sugar Curves—The marked fluctuations in blood sugar curves in the animals receiving identical treatment may be observed in any one or in all of the tables. The variations are so great that mathematical handling of the data is impossible, and consequently the evaluation of results is difficult.

² Hagedorn, H. C., and Jensen, B. N. *Biochem Ztschr* **128** 185 and 207, 1922.

It was found in a series of fourteen well-fed rabbits receiving "small" doses of insulin after the ingestion of dextrose that there resulted a greater depression of the average blood sugar curve than in a group of eighteen animals receiving "massive" doses of the hormone (tables 1, 2 and 3 and chart 1). In view of the enormous differences in the individual reaction of the animals, it does not seem justifiable to draw conclusions beyond stating that there was a "tendency" for the blood sugar levels of well-fed rabbits to be depressed more by "small" doses of insulin than by "massive" ones after the ingestion of dextrose.

Blood Sugar
Mgm
per 100 CC

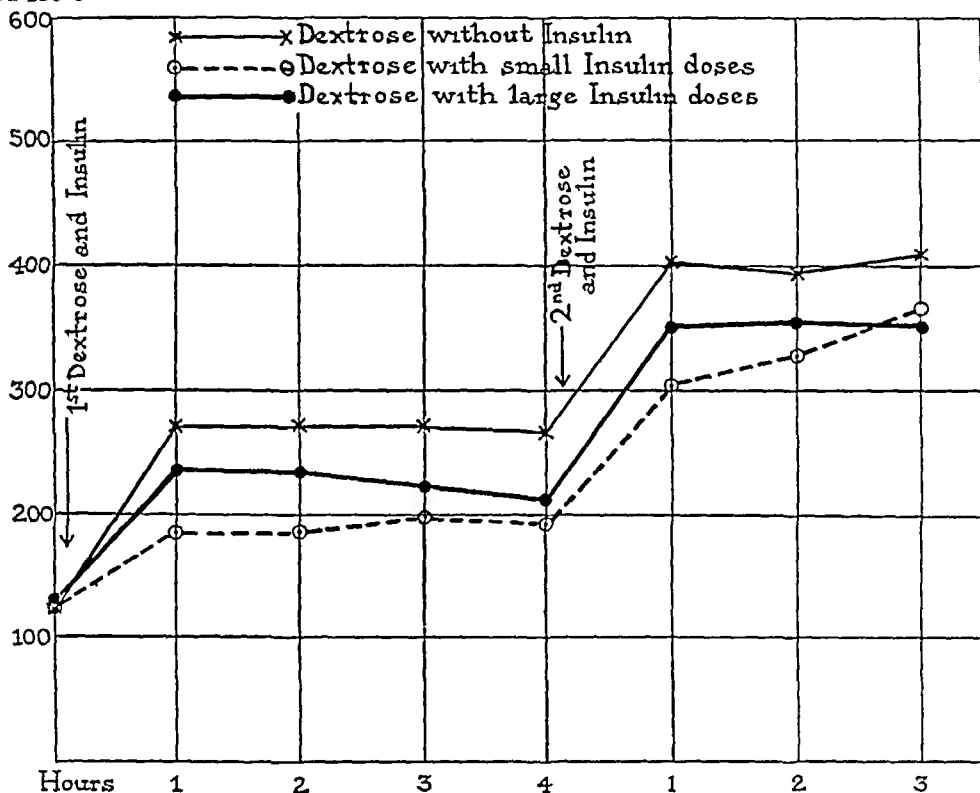


Chart 1—Average blood sugar curves of well-fed rabbits that received (1) dextrose without insulin, (2) dextrose with "small" doses of insulin and (3) dextrose with "massive" doses of insulin. A number of results which were similar to those presented have been omitted from chart 1 because a less reliable method was used for the determination of the blood sugar in the first experiments.

In the group of animals starved for forty-eight hours before the administration of dextrose and insulin, no constant or consistent difference was noted in the response to "small" doses of insulin in contrast to "massive" ones (tables 4, 5 and 6).

Experiments carried on with crystalline insulin (tables 7 and 8) showed no definite differences in the behavior of the blood sugar curves after "small" as compared with "massive" doses of insulin, but the number of animals used was too small to be of significance.

TABLE 1—*Well-Fed Rabbits That Received No Insulin After Feeding of Dextrose*

Date	Rabbit Number	Blood Sugar After First Dextrose					Blood Sugar After Second Dextrose			Liver Glycogen 7 1/2 Hours After First Dextrose, per Cent	Comment
		0 Hr, Mg per Cent	1 Hr, Mg per Cent	2 Hr, Mg per Cent	3 Hr, Mg per Cent	4 Hr, Mg per Cent	1 Hr, Mg per Cent	2 Hr, Mg per Cent	3 Hr, Mg per Cent		
12/26/28	14	131	313	312	332	315	342	426	400	12.4	
12/29/28	17	125	260	206	230	266					Rabbit weak, convulsed and died 1 hour after second administration of dextrose
1/ 2/29	18	125	247	284	300	241	304	278	282	13.1	
1/ 3/29	19	138	245	238	238	253	306	370	422	14.9	
1/ 4/29	20	98	417†	428	428	453	508	483	483	13.1	Slight diarrhea
1/ 9/29	21	122	260	282	282	296	249	313	345	11.3	
1/11/29	22	130	312	307	295	215	570	709	746		Rabbit died before liver was removed was weak and drowsy
8/16/29	72	127	263	237	236	232	624				Grew progressively weaker and died
8/17/29	73	129	243	249	221	238					Neck broken and animal killed at time of second feeding of dextrose
8/17/29	74	127	193	208	236	208	506				Rabbit grew weak and died
8/19/29	75	136	232	199	188	185	206	208	191	11.5	
Average		126	271†	271	271	269	402	395	410	13.2	

* A number of results which were similar to those presented have been omitted from tables 1, 2 and 3 because a less reliable method was used for the determination of the blood sugar in the first experiments

† Approximate value

TABLE 2—*Well-Fed Rabbits Receiving Small Doses of Insulin (Seven Units Per Kilogram) After Each Dextrose Feeding*

Date	Rabbit Number	Blood Sugar After First Dextrose and Insulin					Blood Sugar After Second Dextrose and Insulin			Liver Glycogen 7 1/2 Hours After First Dextrose and Insulin, per Cent	Comment
		0 Hr, Mg per Cent	1 Hr, Mg per Cent	2 Hr, Mg per Cent	3 Hr, Mg per Cent	4 Hr, Mg per Cent	1 Hr, Mg per Cent	2 Hr, Mg per Cent	3 Hr, Mg per Cent		
11/27/28	2	117	166	157	149	147	235	204	204	10.1	Slight diarrhea at end of experiment
12/ 3/28	4	138	108	129	133	135	151	167	195	9.7	Slight diarrhea at end of experiment
12/ 5/28	6	121	122	115	111	126	184	212	268	8.7	
12/11/28	8	123	153	212	210	216	267	271	285	12.8	
12/14/28	10	131	219	228	252	213	280	280	284	7.6	Some diarrhea, liver fibrotic, somewhat dyspneic
12/18/28	12	121	163	181	174	202	221	213	253	5.8	A little dyspneic
8/ 2/29	58	124	207	244	261	248	447	385	728	10.6	
8/ 3/29	60	129	163	131	145	141	287				Rabbit grew restless and weak and then died, slight diarrhea, autopsy negative
8/ 5/29	61	131	253	294	302	278	775	506	510	13.8	
8/ 6/29	63	119	195	198	195	157	336	452			Rabbit became weak and died, slight diarrhea toward end
8/ 7/29	65	138	226	236	243	228	378	470	480	12.7	
8/ 9/29	68	150	245	208	228	219	318	372	398	11.2	
Average		129	185	186	198	193	305	329	364	10.3	

TABLE 3—*Well-Fed Rabbits That Received Massive Doses of Insulin (Seventy-Five Units Per Kilogram) After Each Feeding of Dextrose*

Date	Rabbit Number	Blood Sugar After First Dextrose and Insulin					Blood Sugar After Second Dextrose and Insulin			Liver Glycogen 7 5 Hours After First Dextrose and Insulin, per Cent	Comment
		0 Hr, Mg per Cent	1 Hr, Mg per Cent	2 Hr, Mg per Cent	3 Hr, Mg per Cent	4 Hr, Mg per Cent	1 Hr, Mg per Cent	2 Hr, Mg per Cent	3 Hr, Mg per Cent		
11/26/28	1	124	202	175	133	118	288		221	8 9	
12/ 1/28	3	131	152	143	151	147	300	272	311	8 4	Rabbit weak and dyspneic at end of experiment
12/ 4/28	5	128	331	316	306	304	477	466	392	13 0	Hind legs somewhat weak
12/10/28	7	122	160	218	243	230	354	271	383	6 0	Somewhat dyspneic toward end of experiment
12/12/28	9	130	342	362	356	327	431	449	420	12 5	Somewhat dyspneic toward end of experiment
12/17/28	11	122	196	143	136	133	244	222	216	8 8	
12/19/28	13	132	190	262	293	328	452	430	416	7 2	Rabbit somewhat dyspneic throughout experiment
8/ 2/29	57	110	171	158	153	137					Weak after second administration of dextrose and insulin
8/ 3/29	59	134	241	220	211	206	302	296	328	12 0	
8/ 6/29	62	141	253	244	211	211	322	344	364	12 2	Rather drowsy and had slight diarrhea at end of experiment
8/ 7/29	64	132	204	254	195	172	332	277	286	12 0	
8/ 8/29	66	148	304	226	209	173	276	234	222	13 9	
8/ 9/29	67	145	306	300	292	230	442	612	636	8 5	
Average		131	235	232	222	209	352	352	349	10 3	

TABLE 4—*Fasted Rabbits That Received No Insulin After Dextrose Feeding*

Date	Rabbit Number	Blood Sugar After First Dextrose					Blood Sugar After Second Dextrose			Liver Glycogen 7 5 Hours After First Dextrose, per Cent	Comment
		0 Hr, Mg per Cent	1 Hr, Mg per Cent	2 Hr, Mg per Cent	3 Hr, Mg per Cent	4 Hr, Mg per Cent	1 Hr, Mg per Cent	2 Hr, Mg per Cent	3 Hr, Mg per Cent		
3/22/29	41	110	206	202	188	155	247	247	275	7 3	Slight diarrhea
3/26/29	42	145	400	434	472	408	728	964	1104	2 2	A slight drowsiness for last 3 hours
3/29/29	43	124	225	289	254	244	296	342	358	7 3	
4/ 2/29	44	113	264	275	239	198	213	292	366	5 5	
4/ 9/29	45	122	314	372	364	332	576	636	652	2 6	Weak and sleepy during last 3 hours, questionable slight diarrhea
8/30/29	82	145	298	364	346	300	460	576	552	8 2	
9/ 2/29	83	143	308	386	404	372	486	390	400	11 6	
9/ 2/29	84	132	300	350	340	304	368	412	346	10 1	
Average		129	289	334	327	289	422	482	507	7 0	

Liver Glycogen—A comparison of tables 1, 2 and 3 shows that less glycogen was stored in the livers of animals receiving insulin than in the control rabbits. This is a confirmation of results obtained by many investigators. Whether “massive” doses or “small” doses of insulin were administered was immaterial so far as the glycogen content of the liver was concerned, probably because the “small” dose of 7 units per kilogram was sufficient to produce a maximum effect. In animals starved for forty-eight hours before the administration of dextrose and insulin, there again appeared to be some depression of the glycogen content of

Blood Sugar
Mgm
per 100 CC

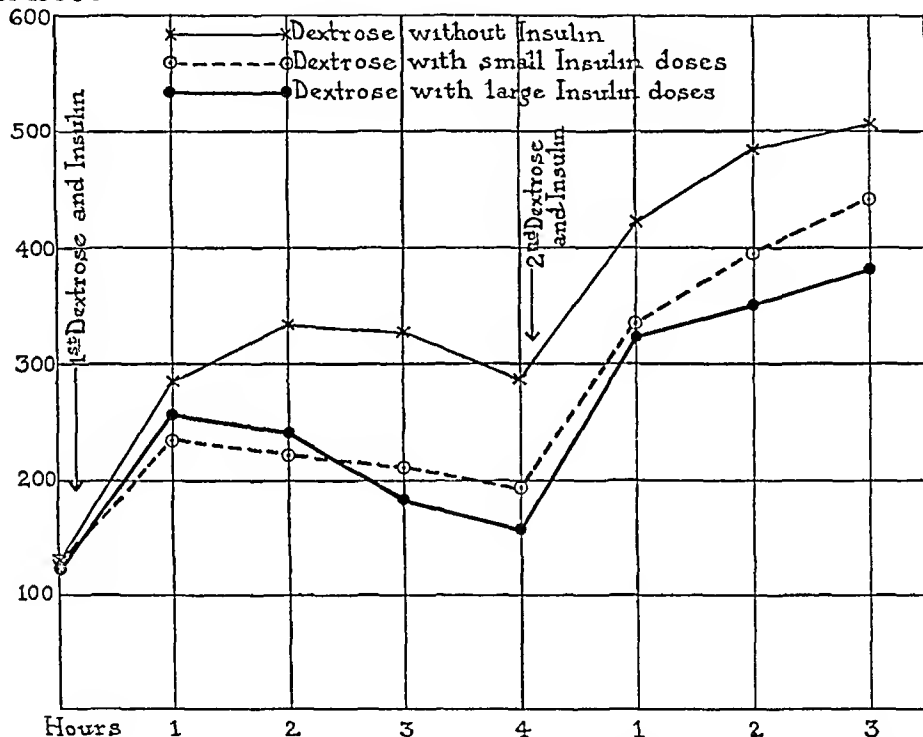


Chart 2—Average blood sugar curves of previously fasting rabbits that received (1) dextrose without insulin, (2) dextrose with “small” doses of insulin and (3) dextrose with “massive” doses of insulin

the liver as contrasted with the animals receiving dextrose alone, as may be observed in tables 4, 5 and 6. The difference in behavior of insulinized and of control rabbits in this group is not as consistent or as striking as in the group of well-fed animals.

Pathologic Examination of Tissues—The variations in weight of the adrenal glands and livers in relation to body weight were so great in the control animals that received dextrose but no insulin that no definite change could be noted in the rabbits receiving either “small” or “massive” doses of insulin. In the histologic studies of the adrenal

TABLE 5—*Fasted Rabbits That Received Small Doses of Insulin (Seven Units Per Kilogram) After Each Feeding of Dextrose*

Date	Rabbit Number	Blood Sugar After First Dextrose and Insulin					Blood Sugar After Second Dextrose and Insulin			Liver Glycogen 7 1/2 Hours After First Dextrose and Insulin, per Cent	Comment
		0 Hr, Mg per Cent	1 Hr, Mg per Cent	2 Hr, Mg per Cent	3 Hr, Mg per Cent	4 Hr, Mg per Cent	1 Hr, Mg per Cent	2 Hr, Mg per Cent	3 Hr, Mg per Cent		
1/25/29	28	131	214	172	137	140	174	418	487	4 6	Somewhat weak the last 2 hours liver slightly fibrotic
1/30/29	30	126	323	378	426	400	728	902	944	7 2	
2/ 5/29	32	128	197	177	168	175	307	340	376	8 2	Weak for last 2 hours
2/ 8/29	34	150	441	274	244	227	392	353	321	7 9	
2/19/29	36	131	158	210	276	258	577	667	703	2 5	Drowsy for last 3 hours
2/26/29	38	134	234	244	227	185	295	366	457	3 5	Rather drowsy
8/23/29	78	113	177	161	134	115	198	205	216	5 7	Stool rather soft, no diarrhea
8/27/29	80	145	247	243	199	172	213	215	353	5 5	
3/19/29	40	119	108	95	89	82	124	106	98	5 6	Stool rather soft, no diarrhea
8/30/29	81	141	255	258	198	182	346				Died 2 hours after second feeding of dextrose and insulin, stool soft
Average		132	235	221	210	193	335	397	440	5 6	

TABLE 6—*Fasted Rabbits That Received Massive Doses of Insulin (Seventy-Five Units Per Kilogram) After Each Feeding of Dextrose*

Date	Rabbit Number	Blood Sugar After First Dextrose and Insulin					Blood Sugar After Second Dextrose and Insulin			Liver Glycogen 7 1/2 Hours After First Dextrose and Insulin, per Cent	Comment
		0 Hr, Mg per Cent	1 Hr, Mg per Cent	2 Hr, Mg per Cent	3 Hr, Mg per Cent	4 Hr, Mg per Cent	1 Hr, Mg per Cent	2 Hr, Mg per Cent	3 Hr, Mg per Cent		
1/23/29	27	126	413*	444	359	308	523	618	698	6 2	
1/29/29	29	133	253	184	128	121	219	189	153	8 5	
2/ 1/29	31	122	309	235	163	131	372	374	458	5 7	
2/ 6/29	33	121	243	202	163	114	270	232	182	6 4	
2/15/29	35	120	166	210	162	169	366	394	461	4 6	Somewhat drowsy for last 3 hours
2/22/29	37		253	290	202	157	372	452	480	5 8	Somewhat drowsy for last 3 hours
8/22/29	76	134	264	211	131	106	181	283	385*	3 8	Weak in hind legs, apparently injured, liver slightly fibrotic
8/23/29	77	132	272	255	228	182	422	502	576	7 2	
8/27/29	79	134	177	134	106	108	238	168	154	5 8	
3/15/29	39	126	216	234	174	178	281	252	226	6 5	
Average		128	257*	240	182	157	324	347	377*	6 1	

* Approximate value

glands, no changes were noted in the structure or in the lipid and chromaffin content that could be attributed to the administration of insulin. No changes were observed in the structure or in the lipid content of the livers of the insulinized animals.

TABLE 7—*Well-Fed Rabbits That Received Small Doses of Crystalline Insulin After Each Dextrose Feeding*

Date	Rab bit Num ber	Blood Sugar After First Dextrose and Insulin					Blood Sugar After Second Dextrose and Insulin			Comment
		0 Hr,	1 Hr,	2 Hr,	3 Hr,	4 Hr,	1 Hr,	2 Hr,	3 Hr,	
		Mg per Cent	Mg per Cent	Mg per Cent	Mg per Cent	Mg per Cent	Mg per Cent	Mg per Cent	Mg per Cent	
4/24/29	47	146	196	185	155	155				Killed accidentally during second administration of dextrose
5/ 1/29	49	154	177	193	200	200	385*	502	528	Weak and dyspneic during last 3 hours
5/ 7/29	51	127	183	234	241	258	340	405	423	
5/17/29	54	151	188	147	137		228	283	220	
5/23/29	55	129	158	140	122	125	239	313	335	Rabbit died during the fol lowing night
Average		141	180	180	171	185	298*	376	377	

* Approximate value

TABLE 8—*Well-Fed Rabbits That Received Massive Doses of Crystalline Insulin After Each Dextrose Feeding*

Date	Rab bit Num ber	Blood Sugar After First Dextrose and Insulin					Blood Sugar After Second Dextrose and Insulin			Comment
		0 Hr,	1 Hr,	2 Hr,	3 Hr,	4 Hr,	1 Hr,	2 Hr,	3 Hr,	
		Mg per Cent	Mg per Cent	Mg per Cent	Mg per Cent	Mg per Cent	Mg per Cent	Mg per Cent	Mg per Cent	
4/23/29	46	131	180	146	123	103				Grew weak and died 1 hour after second feeding of dextrose and insulin
4/30/29	48	140	220	248	231	235				Died in convulsions 1 hour after second feeding of dextrose and insulin
5/ 3/29	50	120	197	217	212	168	356	500		Died in convulsions 2 hours after second feeding of dextrose and insulin
5/14/29	52	108	163	104	68	92				Rabbit killed accidentally during second administra tion of dextrose
5/15/29	53	148	248	210	113	131	293	385*	317	
Average		129	202	185	149	146	325	443*	317	

* Approximate value

General "Toxic" Effects—The amount of dextrose used to produce hyperglycemia was large and was given in concentrated solution. This caused the death of several control animals, all but one of which were in the well-fed group, which began the experiments with already loaded gastro-intestinal tracts. There was no greater mortality among the insulinized rabbits, even though some of them were given injections of

from 300 to 500 units within the space of four hours. Among the series of animals receiving "massive" doses of crystalline insulin, three of five died shortly after the injection of the second dose. Another rabbit in this series was killed accidentally. That death was not due to brucine poisoning, the only possible impurity that might result from the process of insulin crystallization, was shown by the fact that intravenous injections of several milligrams of this alkaloid had no effect on normal animals.

COMMENT

On the basis of the experimental work presented, it seems clear that even enormous quantities of insulin injected intravenously into normal rabbits, protected from hypoglycemia by dextrose feeding, manifest no general toxic effects in the course of seven and one-half hours. This observation is in harmony with the clinical observation of Byworth,³ who used, with satisfactory results, 1,715 units of insulin in the course of thirty-six hours in the treatment of a patient with diabetic acidosis. No explanation can at present be offered for the high mortality of the rabbits treated with "massive" doses of crystalline insulin.

It can be definitely stated on the basis of the work presented in this paper that "massive" doses of insulin do not have a greater effect on the hyperglycemia resulting from the administration of dextrose than do "small" doses. This observation is in accord with the observations of Allan,⁴ who in 1924 showed in depancreatized dogs that the dextrose equivalent per unit of insulin becomes progressively less as the dose of insulin is increased. Our experiments on well-fed rabbits even suggest that "massive" doses of insulin may, not only relatively but actually, have less effect on the hyperglycemia resulting from the administration of dextrose than do "small" doses of the hormone. The fact that no constant differences in the effect of "massive" and "small" doses of insulin were noted in the group of animals previously starved suggests that the amount of glycogen present in the tissues and the state of nutrition may play a significant rôle in the behavior of insulin administered after the ingestion of dextrose. It should be pointed out that the maximal rate of utilization of dextrose resulting from the injection of insulin is probably reached with doses less than 7 units per kilogram, which represents the "small" dose in our experiments.⁵

³ Byworth, H. A. *Brit. M. J.* **1**: 801, 1928.

⁴ Allan, F. N. *Am. J. Physiol.* **67**: 275, 1924.

⁵ Cori, C. F., and Cori, G. T. *J. Biol. Chem.* **70**: 557, 1926.

It has been observed by MacLeod,⁶ Cori⁷ and many others that insulin tends to suppress the deposition of glycogen in the liver after feedings of dextrose. Our work offers confirmation of these results. MacLeod has explained the low values for glycogen in the liver obtained following the injection of insulin by assuming that the small amount of blood sugar, which results from "a sugar vacuum" in the tissues, acts as a stimulus for glycolysis in the liver. This explanation fails to receive support from our experiments, since the liver of the insulinized rabbits contained smaller amounts of glycogen than did those of control animals, in spite of the presence of marked and persistent hyperglycemia. Cori and Cori⁸ recently made observations similar to ours. From the preceding discussion it seems probable that the lower values for glycogen obtained in insulinized animals, in contrast to noninsulinized normal animals, result from an inhibition of the formation of glycogen in the liver or from the slightly lower concentrations of blood sugar.

In 1924, Riddle, Honeywell and Fisher⁹ observed that a single large dose of insulin frequently caused marked swelling of the adrenal glands in pigeons protected from shock by adequate amounts of food. Poll¹⁰ studied the adrenal glands of pigeons and rodents in insulin shock and found a marked decrease in the chromaffin and lipid contents. Kahn¹¹ confirmed Poll's observations, and noted that section of the splanchnic nerves to one gland prevented the changes from developing in this organ. In our work the animals were always protected from shock, and no definite histologic changes were noted in the suprarenal glands. This would suggest that the changes reported by other investigators are dependent on the hypoglycemic reaction and not on the action of insulin per se.

CONCLUSIONS

1. A comparative study has been made of the effects of "small" and of "massive" doses of insulin in well-fed and previously starved normal adult rabbits protected from hypoglycemia by the ingestion of large amounts of dextrose.

6 MacLeod, J. J. R. *Carbohydrate Metabolism and Insulin*, New York, Longmans, Green & Company, 1926.

7 Cori, C. F., and Cori, G. T. *J. Biol. Chem.* **70**: 577, 1926.

8 Cori, C. F., and Cori, G. T. *J. Biol. Chem.* **85**: 275, 1929.

9 Riddle, O., Honeywell, H. E., and Fisher, W. S. *Am. J. Physiol.* **68**: 461, 1924.

10 Poll, H. *Med. Klin.* **21**: 1717, 1925.

11 Kahn, R. H. *Arch. f. d. ges. Physiol.* **212**: 54, 1926.

2 The marked variation in the blood sugar curves of rabbits receiving identical treatment has been emphasized

3 "Massive" doses of insulin do not have a greater effect on the hyperglycemia resulting from administration of dextrose than do "small" doses. Evidence is presented which suggests that in well-fed rabbits "massive" doses of insulin have not only relatively but actually less effect on hyperglycemia than do "small" doses.

4 The storage of glycogen in the liver is suppressed by insulin in spite of the presence of persistent and marked hyperglycemia.

5 In contrast to observations made in the presence of hypoglycemia, no definite histologic changes are found in the adrenal glands of rabbits protected from insulin shock by dextrose. This suggests that the changes observed by other investigators were associated with hypoglycemia, and were not due to the action of insulin per se.

6 The injection of from 300 to 500 clinical units of insulin produces no general "toxic" effect in normal rabbits.

ACUTE TOXIC HEPATITIS (ACUTE YELLOW ATROPHY) DUE TO CINCHOPHEN

REPORT OF A CASE ^{*}

K K SHERWOOD, M D

REDMOND, WASH

AND

H H SHERWOOD, M D

KIRKLAND, WASH

Diagnosis in cases of painless jaundice is always an interesting problem. The two most common causes are, of course, catarrhal jaundice and carcinoma of the head of the pancreas. It so happened that last spring we had on our hospital service at one time three cases of jaundice, all of relatively rare etiology, namely, hepatic syphilis, hereditary hemolytic jaundice and cinchophen poisoning. In this paper we shall briefly review the literature and report the case of cinchophen poisoning.

Chemically, cinchophen is a ring compound containing nitrogen. This occurrence of nitrogen in its double benzene ring undoubtedly is the cause of the occasional development of toxic symptoms. Its therapeutic action is twofold: ¹ first, as a mobilizer of uric acid, it remarkably hastens the excretion of uric acid through the kidneys, and second, it is a distinct antipyretic. This latter effect is marked, since a moderate dose will reduce the temperature of a normal dog an entire degree, whereas in a proportionate dose, sodium salicylate given to normal animals has no effect whatever.

Physiologically, it is excreted rather promptly in the urine, unchanged or slightly oxidized. It has been shown pharmacologically that benzene does not act as a hepatic poison. On the other hand, the inclusion of a nitrogen atom in the chemical ring makes possible the formation of nitrobenzene compounds from it by cleavage.² Trinitrophenol and trinitrotoluene are marked hepatic poisons. Crawford³ studied the

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From the medical service of the Virginia Mason Hospital, Seattle

^{*} Read before the King County Medical Society, Seattle, Nov 10, 1930

1 Furth, O, and Kuh, E. Biochemical Studies on the Absorption of the Ethylester of Paramethylphenyl Cinchoninic Acid and Its Fate in Metabolism, *J Pharmacol & Exper Therap* **38** 1, 1930

2 Brughsch and Horster. Toxicology of Atophan, *Ztschr f d ges Med* **38** 386, 1923, quoted by Rabinowitz, M A. *M Clin North America* **11** 1025, 1928

3 Crawford. TNT Poisoning (Case Report), *Brit M J* **1** 450, 1918

toxic symptoms of trinitrotoluene poisoning, and made the important discovery that in normal munition workers, trinitrotoluene was excreted in the urine. In three cases of acute yellow atrophy in munition workers, however, none was found in the urine, but it was found in the feces. The symptoms of trinitrotoluene poisoning as described by Crawford were essentially those of acute yellow atrophy. There was usually a prodromal stage of from one to three weeks before the onset of jaundice. Contrary to the course of acute yellow atrophy and of cinchophen poisoning, his three patients, although unconscious for many days (one of them for three weeks), recovered, and no residual bad effects could be found. He described the liver as markedly smaller than normal when the patients were in a comatose condition, and on full recovery, as again normal in size. Thus cinchophen poisoning is caused by the abnormal decomposition of the drug within the body into nitrocompounds, and by the failure of the kidneys to excrete these abnormal products of decomposition.

REVIEW OF THE LITERATURE

The drug was first introduced in 1908. It was not until 1913 that reports of adverse results in its use were first published. These dealt with the symptoms in the skin, which usually consist of a rash. The character of this rash is subject to great variation. In some patients it may assume the appearance of the rash in scarlet fever, in others it may be urticarial, and more rarely it is maculopapular. Varieties may or may not be accompanied by purpura-like spots. Several cases have been closely checked, and it has always been demonstrated that once the rash has appeared it will reappear with resumption of the use of the drug, even if a much smaller dose is given. Of the twelve cases with skin manifestations that have been reported, the only fatalities occurred in cases with marked symptoms in the liver.

Strangely enough, since 1913, little mention has been made of lesions in the skin. The first report of jaundice resulting from the use of this drug was that of Schraeder,⁴ in 1922. He reported a series of seventeen cases, all of them mild and nonfatal. Gastro-intestinal symptoms, consisting mainly of nausea and heartburn, with painless jaundice accompanied by pruritis, are the features of the intoxication on which he laid stress. In passing, it is of interest to note that this series is over five times the size of any subsequently reported. Beginning in 1926, several reports are found each year. Langdon Brown's⁵

⁴ Schraeder, K. Cases of Cinchophen Poisoning, *Ugeskr. f. læger* **84** 1141, 1922

⁵ Brown, L. Report on Atophan Poisoning, *Brit. M. J.* **2** 37, 1926

report in July, 1926, seems to have drawn the attention of the scientific world to the possibility of fatal end-results following the administration of this drug. In Germany, several cases were the result of the intravenous administration of a preparation of cinchophen, or of giving an iodine preparation for the study of the gallbladder⁶

We have been able to gather from the available literature⁷ fifty-four cases—fifteen fatal, thirty-nine attended with recovery—clinically complete save in one instance. There seems to be no especial sex or age predilection, if one considers the fact that elderly people present more symptoms for which this drug will be used. All except one of the patients with gastro-intestinal symptoms had jaundice. In a few cases, there was a considerable lapse of time between the cessation of the administration of the drug and the inception of the symptoms. Nausea, heartburn and, in most cases, tenderness in the upper right quadrant of the abdomen preceded the jaundice by from twenty-four hours to five days. There does not seem to be any relation between the daily dose or the length of time the drug was taken and the occurrence of toxic symptoms. This, however, could only be determined by study of a large series in which varying doses would be given over a long period of time. The largest amount taken before toxic symptoms developed was 7,000 grains (455 Gm.), the least, 15 grains (0.97 Gm.), the most taken in one day was 70 grains (4.5 Gm.), the least probably 15 grains, although symptoms developed in several patients when an average dose of less than 15 grains per day was given over a period of weeks.

CLINICAL PICTURE

The clinical picture of cinchophen poisoning is that of acute yellow atrophy of the liver. The first symptoms to be complained of are usually gastric irritability, intolerance and more rarely heartburn. Nausea is almost universally present. It is important to know that these symptoms may arise as late as ten days after the cessation of the administration of the drug. In from one day to a little over a week after these symptoms, the onset of jaundice, biluria, pruritis and sometimes clay-colored stools occur. Pain is usually absent, and when it does occur, it is not extreme. The amount of the drug taken seems to have little bearing on the onset or course of the disease. The jaundice continues to deepen, and usually if it is looked for, a decrease in the

⁶ Hitzengerger, K. Atophan Poisoning (Case Report), *Wien klin Wchn-schr* 40 205, 1927, Singer, S. *Ibid*, p 238. Schwartz, G. *Ibid*, p 238. Haudek, M. *Ibid*, p 239. Klinkert, D. Atophan Poisoning (Case Report), *Therap d Gegenw* 69 140, 1928.

⁷ The articles by Dassen, Miller and Rake (accompanying table) and that by Singer (footnote 6) were not available in the original. These cases were included in the table because they were quoted elsewhere in sufficient detail.

size of the liver can be demonstrated. In the more chronic cases, ascites and splenomegalia may develop. Thus, jaundice usually occurs in the first week of the illness, if by the end of a second week of jaundice, there is not a distinct improvement in the patient's condition, the third week will usually show a marked increase in the symptoms. Jaundice and the toxemia increase, the liver decreases in size, and edema appears in the extremities. Usually by the fourth week the edema begins to become generalized. This is of especially grave significance.

Table on the Cases of Cinchophen Poisoning Reported in the Gastro-Intestinal Literature

Author	Number of Cases	Involvement		Died	Recovered
		Skin	Gastro intestinal		
Anderson, S. O., and Teter, O. P. J. A. M. A. 93 2 (July 13) 1929	1		1	1	
Brown (footnote 5)	2		2	2	
Dassen, R. Semana med 36 368, 1929, abstr J. A. M. A. 92 1563 (May 4) 1929	2		2		2
Drought Worster, C. Brit. M. J. 1 148, 1923	1	1	1		1
Evans, G. Brit. M. J. 2 93, 1926	3		3		3
Frenzel, W. O. Wisconsin M. J. 28 264, 1927	1		1		1
Glover, L. S. Brit. M. J. 2 136, 1926	1		1		1
Haudek (footnote 6, fourth reference)	1		1		1
Herrick, W. W. J. A. M. A. 61 1376 (Nov 11) 1913	1	1	1		1
Hitzenberger (footnote 6, first reference)	2		2	2	
Lowenthal, L. J. A., Mackay, W. A., and Lowe, F. C. Brit. M. J. 1 592, 1928	2		2	2	
McVicar, C. S., and Wier, J. F. M. Clin. North America 12 1526, 1929	1	1	1	1	
Miller, M. Gesellsch. f. inn. Med. u. Kinderh., Feb. 13, 1913, abstr. Therap. Monatschr. 27 468, 1913	1	1			1
Petty, M. J. Brit. M. J. 2 442, 1928	1		1		1
Phillips, J. J. A. M. A. 61 1040 (Sept 27) 1913	5	5			5
Rabinowitz, M. A. M. Clin. North America 11 1025, 1928	2		2		2
Rake, G. W. Guv's Hosp. Rep. 77 229, 1927	1		1	1	
Reichle, H. S. Arch. Int. Med. 44 2 (Aug) 1929	2	2	2	2	
Schraeder (footnote 4)	17		17		17
Schwartz (footnote 6, third reference)	1		1		1
Singer (footnote 6, second reference)	1		1	1	
Sutton, D. C. J. A. M. A. 91 310 (Aug 4) 1928	1	1	1	1	
Wells, O. L. L. Brit. M. J. 2 759, 1926	1		1	1	
Wilcox, W. H. Brit. M. J. 2 273, 1926	3		3	1	2
	54	12	48	15	39

As far as can be ascertained from incomplete case records, no patient in whom this occurred has recovered. Death frequently occurs without the development of edema, however. The patient becomes delirious, then comatose, and dies, presenting a striking picture of hepatic insufficiency. Fever is usually absent, and when present may be accounted for either by a secondary factor, e. g., bronchopneumonia, or by the process for which the drug was given.

Pathologically, the most striking picture is seen in the liver,⁸ which is very small and soft. In the sections, yellow areas the size of a

⁸ Reichle, H. S. TOXIC CIRRHOSIS OF THE LIVER, Arch. Int. Med. 44 2 (Aug) 1929

pinhead are surrounded by soft, red, beefy tissue. Microscopically, one scarcely recognizes the tissue as hepatic. The red areas are found to consist of necrotic debris, small round cells, young connective tissue and fat, free and intercellular. The yellow areas, which contain the only recognizable hepatic cells, are small, and the vast majority of the cells contain a droplet of fat which displaces the greater amount of its area. What remaining cytoplasm there is, is granular. The fatty degeneration is not limited to the liver, however. It is also conspicuous in the heart muscle and in the kidney. Splenomegaly is only seen in the more chronic cases. Edema of the extremities and serous cavities may be great. Primary hepatolysis, therefore, can be accompanied by secondary fatty degeneration of the heart and kidneys. The only exception is the case of Petty,⁹ which at operation showed a pancreatic necrosis. This patient recovered, so no pathologic examination of the liver was possible.

Is there anything that can be done for this condition? Certainly its recognition earlier and the discontinuance of the drug are of primary importance. Graham,¹⁰ in a paper read before the Royal Society in London, emphasized the fact that there is a correct and an incorrect way to administer the drug. He recommended as the correct way, the giving of moderate doses, accompanied by alkalis, for periods of four days, with at least a three day rest between series. It is perhaps significant that only one case of poisoning is reported wherein this regimen was followed. The first gastro-intestinal symptoms in a patient taking a cinchophen preparation should be the signal for its permanent discontinuance—permanent, because it has been repeatedly shown that once symptoms are started, the readministration of even a single dose of the drug may bring on jaundice or symptoms in the skin, if not a fatal outcome. This is preventive therapy. Once jaundice is established, physicians must place their main reliance on dextrose. Mann¹¹ has shown that the cause of death in experimental removal of the liver is due, at least primarily, to the inability of the organism to keep the blood sugar level at its optimum. It is one of the most important functions of the liver to serve as a reservoir for the storage of dextrose so that it can be taken as needed to keep the blood sugar at a nearly constant level. Thus, by frequently giving our patients carbohydrates, we are minimizing the amount of work the liver must perform. Elimination should be aided, and the intake of fluids augmented to the amount

9 Petty, M. J. Atophan Poisoning (Case Report), *Brit. M. J.* 2 442, 1928.

10 Graham, G. Presidential Address, Section of Therapeutics and Pharmacology, *Tr. Roy. Soc. Med.*, October, 1926, quoted by Lowenthal (see table).

11 Mann, F. C. Effects of Complete and Partial Removal of the Liver, *Medicine* 6 419, 1927.

that will be excreted. Rest in bed is, we feel, essential for conserving to the utmost both heart and kidneys, which frequently show a fatty degeneration. Treatment of edema or ascites should be conservative. Sutton's¹² experience with giving a mercury diuretic intravenously illustrates the dangers of treating accumulated fluid in this disease in a routine manner. He administered such a compound with the result that the output of urine, which had been about 1,400 cc per day, promptly dropped to 300 cc for the next three and a half days. Usually in the absence of a fatal ending, results are good. Only one case has been reported in which the patient was left with clinical splenomegalia, and even that was of a mild degree (the spleen was just palpable).

REPORT OF A CASE

History—W. M., a man, aged 27, was first seen on Jan. 4, 1930. His personal and family history were unimportant. The patient complained of a gonorrheal infection and he was given the usual treatment, with seemingly satisfactory results, until January 21, when severe cystitis developed, with almost a constant straining to void. This yielded to irrigations of the bladder, so that by February 1 he was in a satisfactory condition, and it seemed that he was over his troubles. On February 13, however, he began to complain of pain in his ankles and feet, which soon shifted and centered in the left hand and wrist, the pain was so severe that the patient could obtain no rest. With the onset of pain, the temperature rose to 100 F and then to 103 F. After a few days on salicylates and iodides he became comfortable, and the temperature dropped almost to normal. On February 20, he had a chill followed by high temperature, and the recurrence of great pain in the left hand and wrist. The pain was so severe that we gave him a hypodermic of morphine sulphate, $\frac{1}{4}$ grain (0.016 Gm.), thinking that it would give him relief, but it did not, so the following night hyoscine morphine cactin anesthesia was tried. This resulted in a wild delirium. He was put on cinchophen tablets (Schering and Gatz), taking 75 grains (4.87 Gm.) in all. He was free from pain, and his temperature was normal. He remained comfortable for two days, then on the night of February 26 (five days after the administration of cinchophen had been commenced), he had a severe chill and great pain in the region of the right hip. At this time he was also somewhat jaundiced. He was then persuaded to go to the hospital, where he was admitted on February 29, complaining of great pain and marked jaundice.

Course—On March 1, the patient was very uncomfortable. The stools were clay-colored. Examination of the blood revealed hemoglobin, 70 per cent, red cells, 3,860,000, white cells, 14,150 with 79 per cent polymorphonuclears. The Wassermann reaction was negative, and urinalysis showed bile. Both the van den Bergh immediate and delayed reactions were positive. The icterus index was 70. On March 3, the van den Bergh biphasic reaction was positive and the icterus index was 70. The patient was still very uncomfortable on the following day. The van den Bergh direct quantitative reaction was +7.5 mg of serum. The stools were slightly positive from the bile. On March 7, the patient was more comfortable, his condition was less toxic, and the jaundice was beginning to clear.

¹² Sutton, D. C. Acute Yellow Atrophy of Liver Following Taking of Cinchophen (Case Report), J. A. M. A. 91:310 (Aug. 4) 1928.

The next day the van den Bergh direct reaction was $+34$ mg of serum. The temperature ranged from normal to 100°F . Continued improvement was observed on March 10, and on the twelfth, intravenous salicylates were started, which gave marked relief. From the fourteenth to the twenty-sixth, there was gradual improvement on intravenous salicylates and a diet high in carbohydrates.

The patient was discharged on March 28, able to walk on crutches. The jaundice had disappeared.

On April 20, no symptoms had recurred, and he was pronounced clinically well.

CONCLUSIONS

1 The administration of cinchophen is occasionally accompanied by toxic symptoms.

2 These toxic symptoms are of two types, affecting either the skin or the liver.

3 Twelve cases in which there were skin manifestations have been collected from the literature, unless complicated by symptoms in the liver, none of these was fatal. Once cutaneous symptoms appear, the readministration of the drug, even in smaller doses, will cause their recurrence.

4 Forty-eight cases of acute hepatic necrosis were collected from the literature, and one case was added. Fifteen fatalities were reported. Poisoning is apparently due to an abnormal decomposition of cinchophen in the body and its retention, thus corresponding to that occurring in munition workers (due to trinitrotoluene poisoning).

5 Neither the length of time the drug was administered nor any save excessive doses (70 grains) appear to predispose to the onset of toxic symptoms.

6 Pathologically, in the fifteen cases in which death occurred, acute hepatic necrosis (acute yellow atrophy) was found with acute fatty degeneration of the heart and kidneys.

7 Therapy consists of complete rest in bed and the forced feeding of fluids and carbohydrates.

8 Only one patient who recovered retained clinical signs of portal stasis (splenomegalia). Readministration of the drug, even in much smaller doses, will usually produce jaundice immediately.

ESSENTIAL HYPERTENSION

THE DIASTOLIC BLOOD PRESSURE ITS VARIABILITY ^{*}

DAVID AYMAN, M D

BOSTON

There have been in the past many unemphasized observations of diastolic variability both in patients with arterial hypertension and in those with normal blood pressure. In 1911, Schrumpf and Zabel¹ found that in their arteriosclerotic patients, in which group they included those with arterial hypertension, the diastolic blood pressure fluctuated almost parallel with the systolic. They noted diastolic variations up to 35 cm (water sphygmomanometer). Tixier² mentioned that the diastolic tension may undergo important variations. More recently, Fahrenkamp,³ referring to a case of "malignant nephrosclerosis," stated that the diastolic blood pressure curve showed fundamentally the same fluctuations as the systolic curve. Kylin,⁴ in a study of the lability in essential hypertension, does not discuss diastolic lability, but in a charted example of the blood pressure of a patient with essential hypertension he shows a variation of 55 mm of mercury in the diastolic blood pressure during a week's observation. During a twenty-four hour period of study, Mueller and Brown⁵ found a diastolic variation of 40 mm of mercury in a patient with normal blood pressure and a diastolic variation of 70 mm in a patient with essential hypertension. In a patient with "severe benign hypertension," Brown⁶ found a diastolic variation of 48 mm within a five hour period. Frost⁷ and Amiral⁸

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^{*} From the Medical Clinic of the Boston Dispensary, service of Dr Joseph H Pratt, and the Division of Research

1 Schrumpf, P, and Zabel. Die diagnostische Bedeutung der psychogenen Labilität des Blutdruckes, München med Wchnschr **58** 1952 (Sept 12) 1911

2 Tixier, L. Les variations normales et anormales de la tension artérielle humérale, Arch d mal du coeur **12** 337 (Aug) 1919

3 Fahrenkamp, K. Die psycho-physischen Wechselwirkungen bei den Hypertoniekrankungen, Stuttgart, Hippokrates, 1926, p 42

4 Kylin, E. Die Hypertoniekrankheiten, Berlin, Julius Springer, 1926, p 70

5 Mueller, S C, and Brown, G E. Hourly Rhythms in Blood Pressure in Persons with Normal and Elevated Pressures, Ann Int Med **3** 1190 (June) 1930

6 Brown, G E. Daily and Monthly Rhythm in the Blood Pressure of a Man with Hypertension. A Three-Year Study, Ann Int Med **3** 1177 (June) 1930

7 Frost, H M. The Response of the Cardio-Vascular System to Respiratory Exertion, Boston M & S J **191** 853 (Nov 6) 1924

8 Amiral, H H. The Reaction of the Diastolic Pressure to Respiratory Strain, Boston M & S J **191** 863 (Nov 6) 1924

produced, both in patients with normal blood pressure and in those with hypertension, diastolic variations up to 32 mm of mercury by means of respiratory exertion. O'Hare and Walker,⁹ while observing the effect of salt in essential hypertension, found in patients in the wards diastolic variations up to 65 mm. O'Hare stated¹⁰ that excitement might raise the diastolic blood pressure as much as 24 mm. While discussing "emotional hypertension," Stieglitz¹¹ reported an average rise of 29 mm in the diastolic blood pressure of eight patients under emotional strain. Mosenthal and Short¹² and Sigler¹³ separately studied the effect of rest on the blood pressure in essential hypertension by taking the blood pressure of reclining subjects at frequent intervals during total periods of from three to ninety minutes. Mosenthal and Short found in forty of these patients an average drop in diastolic blood pressure of 10 mm of mercury, with ranges of 0 to 30 mm. Sigler did not publish the details of his studies, but he charted a diastolic variation of 50 mm of mercury, occurring in a patient while reclining for eight minutes.

In almost all of the foregoing studies, the problems investigated have not been those of diastolic variability, so that the diastolic variations are hardly more than mentioned. All the observations cited, among many others unquoted, show that there is a significant fluctuation of the diastolic blood pressure in individual cases. These studies do not indicate, however, the great extent to which the diastolic blood pressure may fluctuate in a large number of patients with essential hypertension who have been observed over a moderately long period of time. Such is the nature of the present study.

METHOD OF PRESENT STUDY

During the past two years, I have seen a large group of patients with essential hypertension at frequent intervals in the hypertension clinic of the Boston Dispensary. Of this group, seventy-six patients were chosen for the purpose of the present study. The basis of selection was merely that of regular attendance at

9 O'Hare, J. P., and Walker, W. G. Observations on Salt in Vascular Hypertension, *Arch. Int. Med.* **32**: 283 (Aug.) 1923.

10 O'Hare, J. P. Vascular Reactions in Vascular Hypertension, *Am. J. M. Sc.* **159**: 373 (March) 1920.

11 Stieglitz, E. J. Emotional Hypertension, *Am. J. M. Sc.* **179**: 775 (June) 1930.

12 Mosenthal, H. O., and Short, J. J. The Spontaneous Variability of Blood Pressure and the Effects of Diet upon High Blood Pressure, *Am. J. M. Sc.* **165**: 531 (April) 1923.

13 Sigler, L. H. Spontaneous Nonrhythmic Variations in the Blood Pressure Levels and in the "Silent Gap," *Am. J. M. Sc.* **177**: 494 (April) 1929.

the clinic The diagnosis of essential hypertension was made in the individual case only after at least two months' observation and after obtaining at least five abnormally high blood pressure readings, together with normal renal function tests¹⁴ A few of the patients observed had moderately impaired renal function These have been purposely included in the study and will be referred to later No medication was given during the period of observation utilized for the present investigation

I made all the blood pressure observations by using a mercury sphygmomanometer, the auscultatory method, and the beginning of the fourth sound as an index of the diastolic blood pressure The blood pressure readings were taken in a quiet room while the patient was seated, with his arm resting on an adjacent table The readings were taken at each visit when the patient first sat down and then at intervals of from five to ten minutes over periods varying between five and forty-five minutes In this manner, patients were observed over periods of from two months to two years, although the period of known hypertension ranged in the individual cases from a minimum of seven months to a maximum of fifteen years In determining the total individual diastolic variation during the period of study, the highest diastolic reading was utilized only if it antedated or was taken soon after the lowest diastolic reading In this way, one obviates the criticism that as the disease advances during the course of a year or two, the diastolic blood pressure may rise naturally and an apparent fluctuation appear

OBSERVATIONS

For the purpose of analysis, the seventy-six patients were divided into three groups on the basis of the general height of their systolic blood pressure, group 1 having readings usually above 200 mm of mercury, group 2 usually between 160 and 200 mm of mercury, while in group 3 the systolic blood pressure readings were mostly between 160 mm and the upper normal limits¹⁵ The diastolic blood pressures of group 1 were in general higher than those of group 2, which, in turn, were higher than those of group 3

1 *Total Individual Variations Without Rest Periods*—The total diastolic variations in these three groups ranged from a minimum of 5 mm to a maximum of 66 mm of mercury, with an average variation for the seventy-six patients of 30 mm The average variation of group 1 was 37.5 mm, of group 2, 32.4 mm, and of group 3, 22.5 mm (table 1) In other words, the higher the systolic blood pressure, the greater was the total diastolic fluctuation in these patients The total variation of the diastolic blood pressure in each of the seventy-six patients is shown in chart 1 So far these figures refer only to the total diastolic variation found in the initial blood pressure readings of all visits, excluding the drops due to rest periods

14 Ayman, D Normal Blood Pressure in Essential Hypertension, J A M A 94 1214 (April 19) 1930

15 Hunter, A W Blood Pressure What Affects It? An address before Association of Life Insurance Presidents, Dec 6, 1923

2 *Effect of Rest Periods on the Total Variation*—By including in the total variations the drops in diastolic blood pressure that occurred while the patient sat in a quiet room, it was found that the diastolic variations in the three groups ranged from a minimum of 8 mm to a maximum of 70 mm, with an average of 37 mm (chart 1 and table

TABLE 1—*The Effect of Rest and of the Height of the Systolic Blood Pressure on the Total Diastolic Variation*

	Group 1 24 Patients With Systolic Usually 200 Mm or More	Group 2 22 Patients With Systolic Usually Between 160 200 Mm	Group 3 30 Patients With Systolic of 160 Mm or Less
Total diastolic variation of initial blood pressure readings during total observation	37.5 mm	32.4 mm	22.5 mm
Total diastolic variation of all diastolic readings during total observation (including rest periods)	43.5 mm	37.5 mm	30 mm

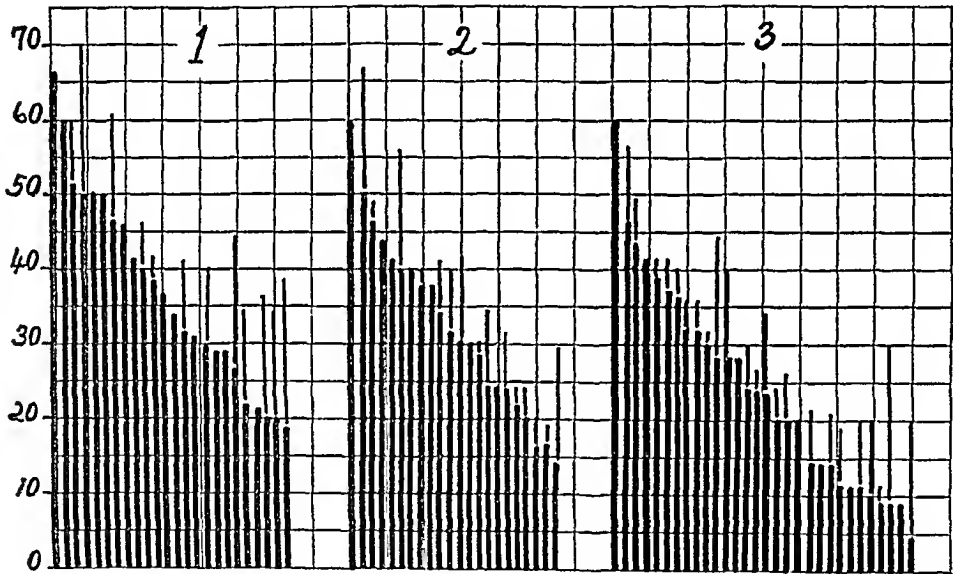


Chart 1—The total variation of the diastolic blood pressure in each of seventy-six patients. Each vertical black band represents the total variation occurring without rest periods. The narrower vertical bands indicate the additional diastolic variation due to rest periods. Groups 1, 2 and 3 correspond to those described in the text.

1) The average variation of group 1 now became 43.5 mm, of group 2, 37.5 mm, and of group 3, 30 mm. Rest periods, therefore, increase the total diastolic variations.

3 *Relation of the Number of Visits to the Amount of Total Variation*—The extent of the total fluctuation in the individual case bears a distinct relation to the total number of visits made by the patient and utilized for the study: the greater the number of visits, the greater

the fluctuation within limits. This is shown in chart 2 which illustrates only the patients in group 1. The same relationship was found to hold true in groups 2 and 3. Practically all patients observed ten or more times had total diastolic variations of 30 mm. of mercury or more.

4 *The Percentage of Variation of the Diastolic as Compared with the Percentage of Variation of the Systolic Blood Pressure*—By taking the highest diastolic blood pressure reading in the individual case, e. g., 150 mm. of mercury, and also the corresponding lowest diastolic reading, e. g., 100 mm., it is possible to express the difference of fluctuation as a percentage fluctuation of 150 mm. By using the same method with

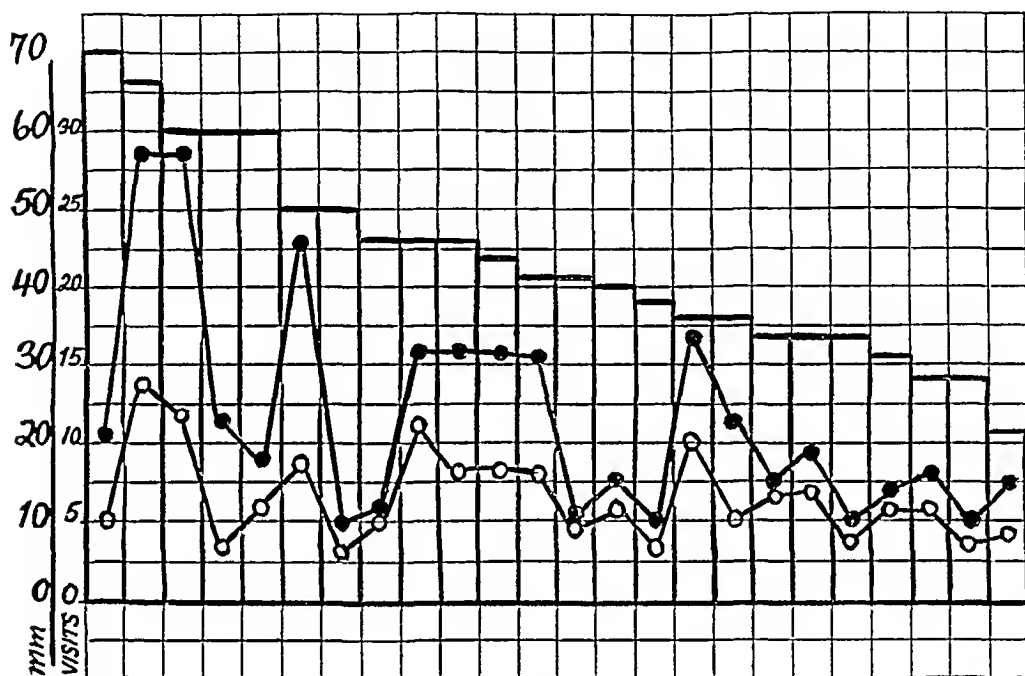


Chart 2—The relation of the number of visits to the degree of total diastolic fluctuation. The chart is a rearrangement of the cases in chart 1 (1) to show the entire diastolic fluctuation in each case. The total number of visits (solid black dots) and the number of visits with rest periods (circles) are plotted in each case.

the corresponding systolic blood pressures, it is then possible to compare the percentage of fluctuations of the systolic and diastolic blood pressures. It is thus seen that a patient whose blood pressure has varied, for example, between 240 systolic and 150 diastolic and 160 systolic and 100 diastolic, has had a percentage fluctuation of 33.3 per cent in both the systolic and the diastolic blood pressures.

In this manner the percentage fluctuations of the systolic and diastolic blood pressures of the seventy-six patients were determined and compared in each patient. It was found that in group 1 the average percentage fluctuation of the diastolic pressure was 32 per cent and of the systolic, 32 per cent, in group 2, the diastolic was 32 per cent and

the systolic was 36 per cent, and in group 3, the diastolic was 26 per cent and the systolic was 27 per cent. The average percentage fluctuation for the three groups was diastolic, 30 per cent and systolic, 31.6 per cent. For practical purposes it may be said that the percentage fluctuation of the diastolic blood pressure was as great as that of the systolic blood pressure.

5 *Maximum Diastolic Variations at Any One Visit*—In order to determine the maximum diastolic variation at any one visit in each patient, it was necessary to utilize only the blood pressure readings taken during visits with rest periods. It was found that the greatest diastolic fluctuation at any one visit was 65 mm and the smallest variation was 4 mm. The average of group 1 was 17.9 mm, of group 2, 13.5 mm, and of group 3, 14.5 mm. The modal distribution of these fluctuations showed that in group 1, 82 per cent of the patients had maximum fluctuations between 15 and 25 mm, in group 2, 81 per cent had maximum variations between 5 and 20 mm, and in group 3, 84 per cent had their maximum between 5 and 20 mm.

6 *The Relation of the Maximum Diastolic Variation at Any One Visit to the Number of Visits with Rest Periods*—Of the patients who made more than five visits with rest periods, 65 per cent (twenty-three) had maximum diastolic variations of more than 15 mm at one of these visits. On the other hand, of the patients who made five or less visits with rest periods, 65 per cent (twenty-seven) had maximum diastolic variations of less than 15 mm of mercury at one of these visits. This indicates that the greater the number of visits with rest periods, the greater the maximum diastolic variation during some one of these visits.

7 *The Relation Between the Maximum Diastolic Variation at Any One Visit and the Time Required for the Variation to Occur*—The maximum diastolic variation at any one visit occurred in 80 per cent of the patients only after ten minutes or more of rest and in 50 per cent of the patients only after twenty minutes or more of rest. However, the amount of maximum variation at any one visit seemed to bear no relation to the length of the rest period. Of the patients who had rest periods of less than ten minutes, 60 per cent had variations of more than 15 mm, of the patients who had rest periods of from ten to twenty minutes in length, 50 per cent had variations of more than 15 mm, and of the patients who had rest periods of more than twenty minutes, 46 per cent had variations of more than 15 mm.

COMMENT

In seventy-six unselected, untreated patients with essential hypertension, the diastolic blood pressure was found to fluctuate widely

TABLE 2—*Analysis of the Seventy-Six Cases of Essential Hypertension in which the Diastolic Blood Pressure Fluctuated*^a

Case	Age	Known Duration of Hypertension, Yr	Diastolic Range During Total Observation	Heart Enlargement by Orthodiagraph	Electrocardiographic Changes, Degree	Changes in Retinal Blood Vessels	Renal Function Impairment
Group 1							
1	51	5 0	150 84	—	—	—+—	—
2	44	3 0	150 90	—	+30	—+—	—
(a) 3	42	2 0	154 94	+	+16	—+—	—
4	50	2 0	160 90	+	+33	+—	—
(b) 5	64	12 0	118 68	+	Fibrillation	++	—
6	40	5 0	140 90	+	+24	+++	—
7	64	4 0	140 80	+		+++	—
8	64	1 0	134 88			+++	—
(a) 9	67	1 3	140 98	—		Cataracts	—
10	70	7 0	120 74	++	+ 6	+++	—
11	50	8 0	130 88	+	0	+++	—
12	51	11 0	136 100	++	— 3	+++	+
13	61	1 2	120 86	—	—	++	—
14	68	5 0	140 94	+	+24	+++	—
(c) 15	50	2 2	140 108	++	+30	+++	—
(b) 16	53	0 6	140 100	+++		+++	—
17	59	2 0	130 102			+++	—
18	46	8 0	138 110	+	—	+++	—
19	61	15 0	124 80		+40	+++	—
20	64	1 5	128 94	+		+++	—
21	69	8 0	122 100	+++		+++	+
22	44	6 0	144 108	+	+35	++	—
23	63	4 1	130 96	++	+20	+++	—
(b) 24	62	3 8	140 102	++			+
Group 2							
1	53	1 0	140 80	—		+	—
2	52	1 5	140 74	+	+38	—	—
3	42	1 5	150 92	+	+38	++	—
4	50	7 0	124 80	—	— 4	++	—
5	54	6 2	136 94	+		—	—
6	63	1 3	128 72			++	—
(a) 7	56	2 0	130 90	—	+25	++	—
8	46	1 5	130 90	+	+ 3	++	—
9	62	5 0	110 72	+	— 2	++	—
10	65	4 0	102 60	—		++	—
11	70	5 6	100 60	—		+++	—
12	75	5 0	102 60	+	+11	+++	—
13	56	6 0	120 90	—		+	—
14	51	6 5	100 70			—	—
15	70	1 6	118 70			—	—
16	68	1 2	108 84	++		+++	—
17	77	6 0	118 80	++	+16	+++	—
18	61	1 5	100 76	+		+	—
(a) 19	69	4 2	100 76	+		+++	—
20	77	7 0	110 90		0	Cataracts	—
21	60	9 0	120 102	—		++	—
22	62	7 5	120 90	—	—14	++	—
Group 3							
1	45	11 0	140 80	+	—16	++	—
2	53	10 0	124 70	—	—	—	—
3	54	4 0	130 82	—	—	++	—
4	52	2 0	110 68	—	+ 8	++	—
5	46	1 5	120 78			++	—
6	54	1 3	110 68	—		+	—
7	75	2 1	108 68	—		++	—
8	56	1 2	100 64	—	—	+++	—
9	45	7 0	112 76	—		++	—

TABLE 2—*Analysis of the Seventy-Six Cases of Essential Hypertension in which the Diastolic Blood Pressure Fluctuated**—Continued

Case	Age	Known Duration of Hypertension, Yr	Diastolic Range During Total Observation	Heart Enlargement by Ortho diagraph	Electro cardiographic Changes, Degree	Changes in Retinal Blood Vessels	Renal Function Impairment
Group 3—Continued							
10	25	1 0	100 68				—
11	74	4 0	104 60	+	—10	+++	—
12	51	5 0	110 70	+-		+++	—
13	49	2 0	120 92	—		++	—
14	70	1 8	104 74	—		++	—
15	19	1 0	98 72				—
16	60	3 5	102 68	—	—	++	—
17	48	1 3	104 80	—	0	++	—
18	52	7 0	110 84		— 6	—	—
19	38	2 2	128 108	—		++	—
20	58	6 2	90 68	—		+	—
21	50	0 5	92 74		—	+++	—
22	44	1 0	110 90	—		++	—
23	30	0 2	110 92				—
24	19	0 8	88 76			—	—
25	46	1 1	120 100	—		+	—
26	52	7 0	108 90	—		+++	—
27	34	0 2	102 90				—
28	43	1 0	120 90	—		—	—
29	56	1 2	104 96				—
30	54	1 0	104 84	—		++	—

* In the table +++ indicates marked cardiac enlargement, or retinal arteriolar sclerosis, ++, moderate cardiac enlargement, or retinal sclerosis, +, slight cardiac enlargement, or retinal sclerosis, under electrocardiographic changes are given the degree of left axis deviation according to the standards of Einthoven

(a) Have had a cerebral hemorrhage

(b) Died of cerebral hemorrhage

(c) Died of cardiac insufficiency

during periods of observation extending in the individual cases up to one and a half years. It might possibly be contended that the author was dealing with a mild type of essential hypertension. Table 2 shows, however, that many of the patients had already been severely injured by the disease.

In this table, the patients have been arranged in the individual order of the three groups in chart 1. It is seen that in group 1 all the patients had marked retinal arteriolar sclerosis,¹⁴ practically all of them had cardiac enlargement determined by the orthodiagraph, and many of them had electrocardiographic abnormalities. Twenty-five per cent, or six patients, have died or have had cerebral hemorrhages. Seventeen per cent, or four patients, show moderate renal damage, as indicated by poor ability in dilution and concentration, together with albumin and casts. Yet the patients in group 1, despite their generally higher levels of blood pressure than those in groups 2 and 3, and despite their advanced changes, including renal, had, both absolutely and by percentage, as great a diastolic variation as those in groups 2 and 3. In group 2 there is a smaller degree of vascular organic changes, yet sufficient to cause cerebral hemorrhage in two patients. There was as great a diastolic fluctuation in group 2 as in groups 1 and 3.

It therefore cannot be denied that patients with even advanced essential hypertension may, and usually do, have marked fluctuations in their diastolic blood pressure from visit to visit. The degree of fluctuation depends to a certain extent on the number of observations made on the patient: the more frequent the observations, the greater the fluctuation recorded. The lowering effect on the diastolic blood pressure of sitting in a quiet room also seems definite and, conversely, the elevating effect of excitement.

It also is seen that in these observations no patient had a fixed, nonfluctuating hypertension. The systolic and diastolic blood pressures fluctuated in all cases, including the few with definite renal involvement. This suggests that, perhaps outside of some cases with extremely advanced so-called malignant hypertension, practically all patients with essential hypertension have fluctuating blood pressures, and as much by proportion, in the diastolic as in the systolic blood pressure.

CONCLUSIONS

The diastolic blood pressure in essential hypertension, when observed frequently and over a sufficiently long period, fluctuates over a wide range. The percentage of fluctuation of the diastolic is as great as that of the systolic blood pressure.

484 Commonwealth Avenue

CINCHOPHEN OXIDATION TEST OF THE FUNCTION OF THE HEPATIC CELLS¹

S S LICHTMAN, M D

NEW YORK

It is the present consensus¹ that none of the current tests of the function of the liver determine accurately the functional capacity of the organ as a whole. The value of the more useful tests, such as the van den Bergh reaction, the icterus index and the Rosenthal test, is vitiated by the presence of obstructive jaundice even of slight degree, because these tests depend on the measurement of the capacity of the liver to excrete bilirubin or bromsulphalein. Yet in the presence of marked obstructive jaundice, the nonexcretory functions of the liver may remain relatively undisturbed. The more common of the so-called metabolic tests of the function of the liver, such as the determination of the tolerance for galactose and levulose, unfortunately do not give uniform results, and at best permit only of qualitative statements.

Therefore, a test that would determine more accurately the degree of functional impairment of the liver in disease must be one that is not materially influenced by disturbances in the excretory functions of the liver. With this criterion in mind, I have studied the metabolism of phenylcinchoninic acid, a substance known to act as a specific stimulant to the hepatic cells and to possess the properties of a "choleretic."²

After the ingestion of cinchophen, a product of oxidation identified as 2-(ortho-hydroxy)-phenyl-quinoline-4-carboxylic acid appears in the urine.³ I have devised a simple colorimetric method for the estima-

¹ Submitted for publication, Nov 13, 1930

² From the Laboratories and the Medical Department of the Mount Sinai Hospital, Service of Dr George Baehr

1 Shattuck, H F, Brown, J C, and Preston, M P. Clinical Value of Some Recent Tests for Liver Function, *Am J M Sc* **170** 510 1925. Murphy, W P. Biliary System Function Tests, *Arch Int Med* **37** 797 (June) 1926, Boston M & S J **194** 297, 1926. Piersol, G M, and Rothman, M M. Practical Value of Liver Function Tests, *J A M A* **91** 1768 (Dec 8) 1928. Cornell, V H. The Bromsulphalein Hepatic Function Test, *Arch Int Med* **44** 818 (Dec) 1929. Foley, E F. The Clinical Value of Tests of Liver Function, *Arch Int Med* **45** 302 (Feb) 1930. Mann, F C, and Bollman, J L. Liver Function Tests, *Arch Path* **1** 681 (May) 1926.

2 Brugsch, T, and Horsters, H. Cholerese und Choleretica. Ein Beitrag zur Physiologie der Galle, *Ztschr f d ges exper Med* **38** 367, 1923, II Hypo- und Hypercholeresen, *ibid* **43** 517, 1924, III Ueber die choleretische Wirkung von Chinolinderivaten, insbesondere der Atophanreihe, *ibid* **43** 717, 1924.

3 Skorczewski, W, and Sohn, I. Ueber einige im Atophanharnen auftretende charakteristische Reaktionen, *Wien klin Wchnschr* **24** 1700 (Dec) 1911.

tion of this compound in urine, which makes it possible to compare this phase of the metabolism of cinchophen in normal subjects and in those presenting definite or suspected evidence of hepatic dysfunction. Observations with this method indicate that in disturbances of the liver a larger percentage of the ingested drug appears in the urine in the form of oxy-cinchophen⁴. The slight oxidation of cinchophen to oxy-cinchophen is apparently carried on even by the diseased cells of the liver.

THE COLORIMETRIC ESTIMATION OF 2 (ORTHO HYDROXY) PHENYL QUINOLINE 4 CARBOXYLIC ACID IN URINE

This method for estimating this substance in small quantities of urine was devised in order to replace the present laborious and less sensitive methods of chemical isolation⁵. It is based on a characteristic stable siskin-yellow color reaction⁶ obtained when a few drops of urine containing oxy-cinchophen are added to concentrated hydrochloric acid.

Preparation of Standard Solutions—A stock solution of 0.2 per cent oxy-cinchophen⁷ in 5 per cent solution of sodium carbonate is prepared, from which are made standard solutions ranging from 0.0002 to 0.008 per cent oxy-cinchophen in concentrated iron-free hydrochloric acid⁸. Such solutions, hermetically sealed in glass tubes approximately 15 mm in diameter, have thus far not faded in a period of fifteen months.

4 In the text the substance 2-(ortho-hydroxy)-phenyl-quinoline-4-carboxylic acid will be referred to as oxy-cinchophen for the sake of brevity.

5 Skorczewski, W., and Sohn, I. Ueber das Verhalten des Atophans im Organismus, *Wien klin Wchnschr* **25** 593 (April) 1912, Stoffwechselversuche bei Atophandarreichung, *Ztschr f exper Path u Therap* **11** 254, 1912. Dohrn, M. Ueber das Verhalten des Atophans im Organismus, *Biochem Ztschr* **43** 240, 1912. Rotter, L. Zur Kenntnis des Atophans und einiger Atophan Derivate, *Ztschr f exper Path u Therap* **19** 176, 1917. Furth, O., and Kuh, E. Biochemical Studies on the Absorption of the Ethylester of Paramethylphenylcinchoninic acid (Tolysin) and its Fate in Metabolism. I The Absorption of Tolysin from the Intestinal Tract, *J Pharmacol & Exper Therap* **38** 57 (Jan) 1930.

6 This color is described (footnote 3) as "Zeisig-Gelb". The siskin (*G. Zeisig*) is a small sharp-billed, chiefly greenish and yellowish finch (*Spinus spinus*) found in the temperate zone in Europe and Asia, allied to the goldfinch.

7 A lot of 2-(ortho-hydroxy)-phenyl-quinoline-4-carboxylic acid was synthesized for me by the Calco Chemical Company, Boundbrook, N. J. It is an orange or yellowish powder, the melting point being 242 C., and it is insoluble in petroleum ether, only slightly soluble in water and benzene and alcohol and more soluble in ether and methyl alcohol.

8 Chemically pure concentrated hydrochloric acid containing traces or approximately 0.00005 per cent of iron may be employed for the test.

Sensitivity of the Test—By this method oxy-cinchophen can be detected in a concentration of 1 500,000, or 0 0002 per cent In lesser concentrations, the reaction with concentrated hydrochloric acid fails to give the characteristic yellow Solutions of 0 0002 per cent of oxy-cinchophen in distilled water are colorless

Colorimetric Properties of the Reaction—The intensity of color of oxy-cinchophen reacting with concentrated hydrochloric acid was found to be directly proportional to the concentration of oxy-cinchophen in the range studied, between 0 04 per cent and 0 0002 per cent This was established by comparing serial dilutions of oxy-cinchophen with permanent standard solutions The color reaches its maximum almost immediately, and it is stable to heat The intensity of color formation is governed by the concentration of hydrochloric acid A minimal concentration of 0 0002 per cent of oxy-cinchophen fails to react with less than 5 per cent of hydrochloric acid Dilutions of hydrochloric acid below 30 per cent result in a slight loss of intensity of color Thus a maximum of 0 8 cc of urine may be added to a final volume of 5 cc of concentrated hydrochloric acid without loss of intensity of color due to the dilution of acid In this concentration of urine the acid suffices to bleach the urochromes so that they are not an interfering color factor

Atypical Reactions—The chromogen identified by Hertel as indolacetic acid,⁹ which is present in many specimens of urine, yields uroscopin, a rose pink substance, when treated with mineral acid This color is unstable, and its formation is accelerated by heat The excretion of this chromogen has been observed to vary in fractional specimens of urine Sometimes it ceases to be excreted entirely When it is present, a urine obtained prior to the ingestion of cinchophen serves as a control Specimens of urine treated with concentrated hydrochloric acid may also give a carmine color^{9a}

The addition of bile to concentrated hydrochloric acid results in colors ranging from orange to green, the transition being accelerated by heat When bile is present in urine, a specimen obtained prior to the intake of cinchophen serves as a control

The presence of blood in the urine gives a faint yellow reaction probably due to the formation of acid-hematin This interferes with the

⁹ Hertel, C A On Indolacetic Acid as the Chromogen of the "Uroscopin" of the Urine, *J Biol Chem* **4** 253, 1908

^{9a} Fearon, W R, and Thompson, A G The Uroscopin Reaction, *Biochem J* **24** 1371, 1930 These authors apply the term uroscopin to a class of indogenide pigments obtained from the condensation of indoxyl with various phenols unsubstituted in the para-position They believe the uroscopin reaction to be more common than the uroscopin reaction (Personal communication)

colorimetric determination of oxy-cinchophen Among several hundred tests, an interfering yellow color reaction, probably due to the formation of the oxides of chlorine, was twice found in the control urine before the ingestion of cinchophen In both instances, the interfering substances were not present on subsequent days

No atypical or interfering color reactions are encountered in urine after the administration of acetylsalicylic acid, sodium salicylate or the ethylester of paramethyl-phenylcinchoninic acid (neocinchophen)

THE OPTIMUM TEST DOSE OF CINCHOPHEN

When a test dose of 0.10 or 0.45 Gm of cinchophen is administered at intervals of two days (table 1), the fraction excreted each time as oxy-cinchophen is fairly constant in normal and abnormal cases But when the dose of cinchophen is increased to 0.90 Gm, great varia-

TABLE 1—*Determination of the Optimum Test Dose of Cinchophen Tests Repeated at Intervals of Two Days*

Case	Test No	Excretion of Oxy Cinchophen in Twenty-Four Hours, Mg		
		100 Mg Cinchophen	450 Mg Cinchophen	900 Mg Cinchophen
1	1	9	84	154
	2	11	75	146
2	1	20	90	185
	2	24	87	167
3	1	16	60	117
	2	20	65	146
4	1	30	110	158
	2	28	102	307
5	1	35	150	325
	2	40	178	202

bility in the relative quantity of oxy-cinchophen excreted on the different test days is observed in abnormal cases (cases 4 and 5), therefore 0.45 Gm of cinchophen has been adopted as the maximum test dose Table 2 illustrates the constancy of the excretion of oxy-cinchophen on repeated tests with this dose in five normal and ten abnormal patients

FACTORS INFLUENCING QUANTITATIVE RESULTS

In order to define the conditions of the test, a study was made of factors that might influence the oxidation of cinchophen and the excretion of oxy-cinchophen

Body Weight—The oxidation of the test dose of cinchophen is independent of body weight within the range of from 44 to 90 Kg in a series of normal subjects (table 3) and within a range of from 31.5 to 88 Kg in a series of abnormal subjects (tables 4 to 10)

Diet—The excretion of oxy-cinchophen is not appreciably influenced by diet Some of the patients were observed while on a mixed

hospital diet, others were observed while on a diet high in carbohydrates (500 Gm per day) Excessive intake of water may result in a diminished excretion of oxy-cinchophen probably due to a decreased rate of absorption from the bowel

Medication—Morphine and codeine, as well as cathartics, seem to decrease the excretion of oxy-cinchophen, probably by interfering with the absorption of cinchophen from the bowel The actions of insulin and epinephrine modify the results of the test, the former by decreasing the excretion of oxy-cinchophen, the latter by sometimes increasing it The simultaneous administration of sodium salicylate, acetylsalicylic acid or phenyl-ethyl-barbituric acid in therapeutic doses does not alter quantitative results

TABLE 2—*Comparison of Quantitative Results in Repeated Tests, Standard Oral Dose of 0.45 Gm*

Case	Test No	Date of Test	Excretion of Oxy Cinchophen in 24 Hr, Mg	Case	Test No	Date of Test	Excretion of Oxy Cinchophen in 24 Hr, Mg
1	1	1/25/30	31	8	1	4/30/30	150
	2	2/ 7/30	50		2	5/ 2/30	178
2	1	3/28/30	76	9	1	1/27/30	167
	2	1/16/30	58		2	2/ 1/30	129
3	1	2/20/30	84	10	1	3/27/30	154
	2	3/11/30	65		2	3/28/30	186
	3	3/15/30	68	11	1	2/13/30	176
	4	3/17/30	68		2	2/17/30	192
4	1	2/19/30	68		3	2/23/30	207
	2	3/ 2/30	36	12	1	5/13/30	130
5	1	3/ 1/30	75		2	5/17/30	163
	2	3/ 7/30	81	13	1	5/ 9/30	375
6	1	4/30/30	75		2	5/15/30	353
	2	5/ 2/30	84	14	1	2/14/30	162
7	1	5/ 1/30	110		2	2/22/30	176
	2	5/ 2/30	102	15	1	5/ 9/30	118
					2	5/17/30	101

Extrahepatic Disease—Marked impairment of renal function interferes with the excretion of oxy-cinchophen Lesser degrees of renal impairment delay the excretion of oxy-cinchophen but do not appreciably influence the amount excreted over a period of twenty-four hours

High intestinal obstruction interferes with the absorption of cinchophen Malnutrition of long standing interferes with the accuracy of the test, possibly also because of diminished absorption of the drug Drainage of ascitic fluid through the wound of an external abdominal paracentesis results in a diminished excretion of oxy-cinchophen

Body Temperature—The excretion of oxy-cinchophen bears no apparent relationship to the body temperature at the time of the test (a range of from 98 to 104.2 F was studied—tables 4 to 9)

Routes of Administration—A comparison between the oral and the intramuscular routes of administration of cinchophen was made. For the latter, a standard dose of 0.45 Gm of cinchophen sodium was employed. The intramuscular method gave a larger excretion of oxy-cinchophen in seven of ten cases and a lesser excretion in three cases. Repeated intramuscular tests on the same subject did not give uniform results. The inconsistency of the results obtained by the intramuscular route are probably due to an inconstant rate of absorption from the site of injection.

Antemortem Determinations—Tests made one, two or three days before death were usually found to give a definitely diminished excretion of oxy-cinchophen. Under these conditions the normal as well as the markedly diseased cells of the liver may lose even the capacity to convert cinchophen to oxy-cinchophen.

SITE OF OXIDATION OF CINCHOPHEN

It is generally assumed that cinchophen is oxidized by the cells of the liver, although no adequate proof has been presented. Rotter¹⁰ found no evidence of oxidation of cinchophen by the dog's liver and suggested that the liver of animals was different in this respect from that of human beings. In the present research her work was repeated with modifications, and negative results were also obtained.

These experiments consisted in testing colorimetrically the filtrates of suspensions of cells of crushed muscle, lung, liver, kidney, spleen, heart and intestine of freshly killed rabbits that had been receiving intramuscular injections of cinchophen and were excreting oxy-cinchophen at the time they were killed. Similar suspensions of cells were also incubated at 37 C and aerated, after the addition, in vitro, of a buffered solution of cinchophen. However, hemolyzed blood contained in the control filtrates of the lung and liver gave interfering color reactions.

Indirect evidence that the liver is the site of oxidation of cinchophen in human subjects was obtained by comparing the time of appearance and the concentration of oxy-cinchophen in the urine and in bile obtained by transduodenal drainage. Bile aspirated before the intramuscular administration of cinchophen served as a control. The procedure for the detection of oxy-cinchophen in bile is the same as that for urine. In four subjects observed, oxy-cinchophen appeared in the bile from one-half to one hour before it appeared in the urine. In one instance it appeared in the bile at the end of one and a half hours, and in the other three subjects it appeared at the end of two hours. In two

10 Rotter (footnote 5, third reference)

instances it was found in the same concentration in the bile as in the urine and in the other two in higher concentrations in the bile. It appears that oxy-cinchophen is excreted earlier in the bile than in urine and sometimes in higher concentrations.

Oxy-cinchophen could not be demonstrated by my method in the blood plasma following the standard dose given orally, although when it was added to blood plasma it could be detected in the same concentrations as in urine. Therefore, there is no appreciable threshold of excretion of this substance.

Additional evidence that the liver cells are responsible for the conversion of cinchophen to oxy-cinchophen was obtained by the following experiment. In two rabbits under ether narcosis, all of the vessels to the liver and the common bile duct were clamped, and then 2 cc of cinchophen sodium was given intravenously. They survived two hours and did not show the slightest trace of oxy-cinchophen in the urine. Two control rabbits, similarly treated, save that in one the vessels to the liver were not occluded, and in the other only the vessels to the left lobe were clamped, showed traces of oxy-cinchophen in the urine at the end of two hours.

HEPATO-TOXIC ACTION OF CINCHOPHEN

Objection may be raised to the use of cinchophen as a test substance in patients with hepatic disorders in view of the recent reports of damage to the liver ascribed to its administration in therapeutic doses.¹¹ There is evidence, however, that a single or even repeated standard test doses of 0.45 Gm are not toxic, even in the presence of severe damage of the liver. Studies were made on a patient with degeneration of the liver attributed to the ingestion some time before of approximately 18 Gm of cinchophen in a period of eighteen days. During the period of severe jaundice, fever and drowsiness, with an icteric index of 100, the test showed an excretion of 375 mg of oxy-cinchophen on the test dose of 0.45 Gm, the maximum excretion thus far obtained in these studies. One week later, with slight clinical improvement, the excretion was 353 mg in twenty-four hours, sixteen days later, with marked clinical improvement, 141 mg. As will be demonstrated in cases of disease of the liver, excretions above 300 mg signify severe damage of the liver. Thus in this case ascribed to the hepatotoxic action of cinchophen, three doses of 0.45 Gm of this substance given at intervals of approximately a week had no toxic action and did not

¹¹ Reichle, H. S. Toxic Cirrhosis of Liver Due to Cinchophen, *Arch Int Med* **44** 281 (Aug) 1929. Rabinowitz, M. A. Atrophy of the Liver Due to Cinchophen Preparations, *J A M A* **95** 1228 (Oct 25) 1930.

delay clinical and functional recovery. However, I do not advise the performance of the tests in this type of case.

Similar observations have been made in all the cases of disease of the liver that have been studied. Thus far no instance of untoward effects attributable to the cinchophen employed in the test has been encountered. When the disturbance of the liver is due to a relatively benign process, such as in the mild forms of so-called catarrhal jaundice, resolution takes place simultaneously with the administration of repeated test doses of cinchophen. In fact, in many instances a decrease in the intensity of the jaundice is noted on the day following the test, which may be due to the choleretic action of the drug.

Further evidence of the nontoxicity of the test dose of cinchophen was obtained by a comparison of the icteric index before, during and after its administration. Four patients were studied, of whom three had latent jaundice. The first, with a normal index (4), showed no change during or after the administration of two doses of 0.45 Gm., after the administration of two further doses of 0.9 Gm. each, the index was 5 and 6, respectively. The second case (duodenal ulcer), with an initial icteric index of 10, showed a slight rise to 12 after a single dose of 0.45 Gm. Twenty-four hours after a total of 2.7 Gm. of cinchophen had been given within seven days, the icteric index had dropped to 8. In the two remaining cases (pneumonia and cirrhosis of the liver) the initial indexes of 10 rose to 15 and 20, respectively, after the test dose, but a prompt return to indexes even below the original levels (5 and 9, respectively) was noted. The temporary rises observed after the test dose may possibly be physiologic, for the same phenomenon has been observed in normal persons under the stimulation of a test for dextrose tolerance.¹² A similar slight temporary increase in serum bilirubin followed by a rapid decline was noted by others following the administration of cinchophen in the treatment for catarrhal jaundice and for icterus due to cystadenoma of the bile duct.¹³ The prompt return to the original index following the administration of two test doses and two larger doses, 2.75 Gm. of cinchophen in all, over a period of seven days encourages the belief that the excretory function of the liver is not impaired by the procedure.

A study of the amino-acid content of the blood plasma in one normal patient and one abnormal patient before and immediately following a test dose of cinchophen revealed no change in the deamination

¹² Bernheim, A. R. The Significance of Variations of Bilirubinemia, *Arch Path* **1** 747 (May) 1926.

¹³ Grunenberg, K., and Ullmann, H. Atophan Wirkung bei Erkrankungen der Leber und der Gallenwege, *Med Klin* **20** 663 (May 18) 1924.

function of the liver The Folin colorimetric method¹⁴ was employed, the test was made in duplicate, and the average results were recorded In the normal case, the amino-acid nitrogen content of the blood was 51 mg per hundred cubic centimeters before the administration of cinchophen and 5 afterward, in the abnormal case, 6.35 mg before and 4.9 after

Experimentation on animals also failed to reveal any hepatotoxic effect of cinchophen Six rabbits weighing approximately 2 Kg each, receiving 0.45 Gm of cinchophen sodium intramuscularly daily over a period of three weeks, with or without daily doses of 0.5 cc of epinephrine administered subcutaneously, maintained their appetite and weight and showed no gross evidence of degeneration of the liver Only those that were starved showed some loss in weight The negative observations on animals, however, prove nothing regarding the susceptibility of human beings to cinchophen

It is of interest to note that the therapeutic use of cinchophen has been recommended in cases of hepatic disease with jaundice¹⁵

THE FATE OF CINCHOPHEN IN THE ORGANISM

It was known to the original investigators of the actions of this drug¹⁶ that it is readily destroyed in the organism Following the administration of 3 Gm of cinchophen daily for three days to a human being, they found that approximately 5.5 per cent reappeared in the urine unchanged By improved chemical methods, the absorption of cinchophen from the bowel of the dog has been found to be practically a quantitative one¹⁷ The principal conversion product of the metabolism of cinchophen following large doses of the drug is 2-(ortho-hydroxy)-phenyl-quinoline-4-carboxylic acid (oxy-cinchophen) Rotter^{17a} isolated in substance 0.2732, 1.515 and 1.484 Gm, respectively, of this substance from the urine of three patients who had each ingested 2 Gm of cinchophen in doses of 1 Gm, an hour apart Skorczewski and Sohn¹⁸ stated that following the prolonged administration of

14 Folin, O A New Colorimetric Method for the Determination of the Amino-Acid Nitrogen in Blood, *J Biol Chem* **51** 377, 1922

15 Umber, F, in Mohr, L, and Staehlin, R *Erkrankungen der Leber Handbuch der innere Medizin*, ed 2, Berlin, Julius Springer, 1926, p 1 Slobozianu, H Die Behandlung des Ikterus der Neugeborenen, *Arch f Kinderh* **77** 58 (Dec) 1925

16 Nicolaier, A, and Dohrn, M Ueber die Wirkung von Chinolincarbonsäure und ihre Derivate auf die Ausscheidung der Harnsäure, *Arch f klin Med* **93** 331, 1908

17 Furth and Kuh (footnote 5, fourth reference)

17a Rotter, L Zur Kenntnis des Atophans und einiger Atophan Derivate, *Ztschr f exper Path u Therap* **19** 176, 1917

18 Skorczewski and Sohn (footnote 5, first reference)

cinchophen oxy-cinchophen disappears from the urine Under such conditions, the catabolism of cinchophen is probably altered¹⁹

The author compared the daily excretion of oxy-cinchophen in the urine following the ingestion of 0.1 Gm of cinchophen, and 0.1 Gm of oxy-cinchophen, respectively, in four normal subjects and found that the excretion was approximately the same for both, the observations were somewhat higher in all instances with the latter substance In three cases of disease of the liver, a comparison showed that there was an increase in the excretion of oxy-cinchophen following the ingestion of 0.1 Gm of oxy-cinchophen corresponding to that found following the ingestion of the same amount of cinchophen This would indicate that the increase in the excretion of oxy-cinchophen encountered in impairment of hepatic function is probably due to interference in the catabolism of cinchophen beyond the state of oxy-cinchophen The preliminary slight oxidation of cinchophen to oxy-cinchophen is apparently carried on even by the diseased cells of the liver

CLINICAL APPLICATION OF THE TEST FOR HEPATIC FUNCTION

Collection of Urine—The routine procedure for the performance of the test in hospital practice is as follows A routine specimen is obtained at 5 a m At 6 a m, 0.45 Gm of cinchophen contained in a pharmaceutical gelatin capsule is administered to the patient The patient is given his usual diet, and only a moderate amount of fluids is allowed Fractional quantitative specimens are obtained at 10 a m, 12 a m, 2 p m, 4 p m, 6 p m, 10 p m, and all the urine between 10 p m and 6 a m the following morning is saved as a final specimen Random voidings are also saved When accurate measurement of the volumes of the fractional specimens can be depended on, only samples need be saved in ordinary test tubes During the test the patient should receive no morphine, codeine, insulin, epinephrine, cathartic or enema, or any medication that might affect the absorption or oxidation of cinchophen For the correct interpretation of the test it is essential that the urine be collected quantitatively over the twenty-four hour period and that the patient receive and retain the standard dose Vomiting vitiates the results When the patient is unable to void at the specified hour, a statement to that effect is recorded The determination is best made on fractional specimens rather than on a pooled twenty-four hour specimen, because dilution may interfere with the detection of the substance

Colorimetric Estimation of Oxy-Cinchophen—If the urine contains bile or albumin, from 5 to 10 cc of each specimen is heated to boiling and filtered In the absence of bile or albumin, the samples need only to be filtered, 0.2 cc of each filtrate is then added to concentrated hydrochloric acid to make a total volume of 5 cc, the mixture is shaken and brought to a boil If the yellow color of the reaction does not develop, 0.4, 0.6 or 0.8 cc, respectively, of urine is added to concentrated hydrochloric acid to make a final volume of 5 cc and similarly treated

¹⁹ For further oxidation products of cinchophen excreted in the urine, see Dohrn (footnote 5, second reference), or produced in vitro, see Bohm, R, and Bournot, K Ueber die Phenyl-chinolin-4-carbonsäure (Atophan) und ihre Oxidationsprodukte, Ber d deutsch chem Gesellsch 48 1570 (Sept) 1915

The control urine, obtained at 5 a m, prior to the administration of cinchophen, is treated identically

It is sometimes necessary to prepare several control tubes with the aforementioned proportions of urine in order to match the test solution, owing to the fact that the concentrations of the indolacetic acid or bile responsible for atypical reactions vary in the fractional specimens

The heated mixtures are allowed to stand for approximately thirty minutes before reading by comparison with permanent standard solutions in a comparator block fitted for four tubes, approximately 15 mm in diameter, in two rows, and viewed against diffuse daylight through ground glass. The control is placed behind the standard solution and a tube of concentrated hydrochloric acid behind the test solution. When a test solution directly matches any of the standards, the control tube is not placed behind the standard. In the presence of bile, better comparison of color is often obtained when only 0.1 cc of urine is added to a final volume of 5 cc of hydrochloric acid.

The presence of blood in the urine interferes with the test owing to the development of the yellow color of acid-hematin when added to hydrochloric acid.

Calculation—The percentage of oxy-cinchophen determined colorimetrically represents the concentration of this substance in 0.1, 0.2, 0.4, 0.6 and 0.8 cc of urine, respectively, diluted to a final volume of 5 cc. It must be multiplied by the respective dilutions, 50, 25, 12.5, 8.33 or 6.25 to obtain the percentage of oxy-cinchophen in the original urine. The result for twenty-four hours is expressed in milligrams as well as in the percentage of the test dose excreted as oxy-cinchophen. This percentage is calculated on the basis of a theoretical conversion of 450 mg of cinchophen into 480 mg of oxy-cinchophen.

Repetition of the Test—When the test is to be repeated for confirmation or in order to observe the progress of a case, it is advisable to allow at least one day between tests.

QUALITATIVE AND QUANTITATIVE STUDIES ON THE EXCRETION OF OXY-CINCIOPHEN IN SUBJECTS WITHOUT HEPATIC DYSFUNCTION

The time of appearance and disappearance of oxy-cinchophen in the urine following the ingestion of a standard dose of 0.45 Gm of cinchophen was studied in twenty-five subjects over a period of thirty-six hours. Fractional specimens were collected every hour during the first six hours, every two hours in the next six hours, and single specimens at the end of eighteen, twenty-four, thirty and thirty-six hours, respectively. Oxy-cinchophen appeared in the urine in the second or third hour. Its excretion was completed in all cases by the twenty-fourth hour, in the majority of cases by the eighteenth hour and in many cases at the end of twelve hours. In only two cases was a trace of oxy-cinchophen found in the urine voided at the end of twenty-four hours.

The amount of oxy-cinchophen excreted in the urine after the ingestion of a standard dose of 0.45 Gm of cinchophen was determined in a series of fifty selected normal patients (table 3). The quantities of oxy-cinchophen excreted over a period of twenty-four hours varied

TABLE 3—*Excretion of Oxy-Cinchophen in Urine in Twenty-Four Hours in Fifty Selected Cases Without Hepatic Dysfunction, Test Dose of 0.45 Gm of Cinchophen, Rate of Excretion, Relation of Excretion to Body Weight*

Case	Body Weight, Kg	Oxy-Cinchophen in Fractional Specimens, per Cent	Excretion of Oxy Cinchophen in Second 12 Hours, Mg	Total Excretion of Oxy Cinchophen in 24 Hours		Diagnosis
				Mg	Per Cent	
1	57	0 0088 0 0250	0	53	14 0	Bronehopneumonia, bilateral con valescent
2	72	0 0044 0 0088	0	88	18 0	Syphilis, stricture of rectum
3	?	0 0025 0 0125	5	63	13 0	Chyluria
4	44	0 0050 0 0250	0	61	17 0	Neoplasm of pharynx, pituitary gland and stomach
5	65	0 0040 0 0250	0	90	19 0	Polyarthrititis (nonrheumatic)
6	52	0 0025 0 0125	45	97	20 0	Mitral stenosis and insufficiency
7	85	0 0044 0 0250	13	55	11 0	Obesity, hypertension
8	44	0 0050 0 0200	45	88	18 0	Lobar pneumonia (convalescent), pulmonary tuberculosis
9	50	0 0100 0 0175	0	84	17 5	Atherosclerotic heart disease
10	80	0 0025 0 0063	9	59	12 0	Bronchopneumonia (convalescent), hypertension
11	56	0 0025 0 0044	0	31	6 5	Secondary anemia
12	56	0 0025 0 0250	28	90	19 0	Typhus fever (convalescent)
13	70	0 0044 0 0088	36	68	14 0	Coronary artery disease, paronychia
14	55	0 0025 0 0050	24	58	12 0	Subacute bacterial endocarditis
15	?	0 0050 0 0125	9	70	14 5	Subacute bacterial endocarditis
16	52	0 0050 0 0125	0	57	12 0	Infectious arthritis, tonsillitis
17	83	0 0063 0 0125	0	71	15 0	Essential thrombocytopenic purpura
18	53	0 0050 0 0250	0	87	18 0	Mitral stenosis and insufficiency
19	57	0 0025 0 0125	0	77	16 0	Erythema nodosum, tonsillitis
20	74	0 0044 0 0125	0	47	10 0	Coronary sclerosis
21	71	0 0025 0 0088	23	88	18 0	Coronary artery thrombosis
22	77	0 0025 0 0125	0	44	9 0	Benign neoplasm of bronchus
23	59	0 0050 0 0125	26	63	13 0	Hypertension, atherosclerosis
24	75 5	0 0050 0 0088	?	73	15 0	Meningococemia, chronic arthritis
25	79	0 0088 0 0175	0	43	9 0	Postoperative hernia
26	89	0 0088 0 0250	0	91	19 0	Obesity, hypertension
27	58	0 0044 0 0250	13	82	17 0	Lobar pneumonia (convalescent)
28	61	0 0044 0 0125	24	85	17 5	Erythema nodosum
29	61	0 0050 0 0500	26	80	17 0	Hypertension, atherosclerosis
30	73	0 0125 0 0125	0	47	16 0	Coronary artery thrombosis
31	76	0 0025 0 0088	18	60	12 5	Hypertension, diabetes
32	50	0 0175 0 0500	0	90	19 0	Diabetes mellitus, coronary artery disease
33	?	0 0125 0 0250	0	91	19 0	Sinus following empyema of thorax
34	44	0 0050 0 0125	18	61	12 5	Aortic insufficiency, nasopharyngitis
35	66	0 0063 0 0125	0	52	11 0	Secondary anemia
36	59	0 0044 0 0500	30	60	12 5	Hyperthyroidism, hypertension
37	66	0 0016 0 0500	0	74	15 5	Delirium tremens, chronic alcoholism
38	50	0 0050 0 0125	24	54	11 0	Hypertension, coronary artery dis ease, secondary anemia
39	90	0 0040 0 0088	16	60	12 5	Syphilis, hematemeses
40	?	0 0050 0 0250	0	64	13 5	Psychoneurosis
41	50	0 0044 0 0050	45	90	19 6	Carcinoma of nasopharynx
42	50	0 0050 0 0250	0	61	12 5	Secondary anemia
43	70	0 0025 0 0200	23	84	17 5	Coronary thrombosis
44	56	0 0025 0 0200	0	95	20 0	Gastric ulcer, hour glass stomach
45	51	0 0050 0 0250	24	84	17 5	Perisigmoiditis
46	68	0 0050 0 0050	48	78	16 0	Angina pectoris, herpes zoster
47	56	0 0050 0 0375	0	79	16 5	Neurocirculatory asthenia
48	58	0 0025 0 0125	23	84	17 5	Essential hypertension, herpes zoster
49	56	0 0050 0 0000	40	53	11 0	Carcinoma of pharynx
50	60	0 0050 0 0375	0	88	18 0	Acute aseptic lymphocytic meningitis

between 30 and 100 mg, which represents approximately from 7 to 21 per cent of the test dose. The concentration of oxy-cinchophen in fractional specimens of urine varied between 0.0013 and 0.025 per cent (in four cases). In all but two cases the major amount was excreted in the first twelve hour period. In about one half of the cases there was no excretion of oxy-cinchophen in the second twelve hour period. In one half of the remaining cases less than one third of the total amount was excreted in the second twelve hour period.

QUALITATIVE AND QUANTITATIVE STUDIES ON THE EXCRETION OF OXY-CINCHOPHEN BY PATIENTS WITH HEPATIC DYSFUNCTION

The amount of oxy-cinchophen excreted in the urine after the ingestion of a standard dose of 0.45 Gm. of cinchophen was determined in a series of 100 selected patients with hepatic dysfunction (tables 4 to 10).²⁰ The quantities of oxy-cinchophen excreted over a period of twenty-four hours varied between 100 and 375 mg, which represents approximately from 21 to 78 per cent of the test dose. The concentration of oxy-cinchophen in fractional specimens of urine varied between 0.0013 and 0.1 per cent. In nine instances a major amount was excreted in the second twelve hour period. In slightly more than one half of the cases less than one third of the total excretion occurred in the second twelve hour period.

Compared to the series of normal patients, the patients with pathologic conditions show a definitely greater total excretion, at times a higher concentration in fractional specimens and a tendency to a more prolonged excretion of oxy-cinchophen.

Although oxy-cinchophen first appeared in the urine in the second rather than in the third hour more often in the pathologic cases than in the normal subjects, this observation was not proportional to the severity of the functional disturbance and seemed to be of no diagnostic import. In two patients with mild functional disturbance, excretion was observed within the first hour.

The maximum excretion per hour both by normal subjects and by persons with pathologic conditions occurred between the sixth to the tenth hour after the intake of cinchophen. This coincides with the period following the midday meal and may be of physiologic significance.

When the progress of the disease seemed to be clinically stationary, repeated tests gave almost the same figures. Whenever the disturbance of function of the liver was clinically progressive or regressive, corre-

²⁰ Dr. Leo Kessel and Dr. Richard Lewisohn gave me permission to study some of these cases from their respective services.

sponding results were usually obtained that gave a fairly accurate indication of the increase in severity or of improvement

These observations indicate that the excretion of oxy-cinchophen after the administration of a test dose of 0.45 Gm of cinchophen may be used as an index of hepatic function. The results of the test may be expressed in milligrams excreted or in percentage of the test dose excreted in the urine as oxy-cinchophen. Thus an excretion of more than 100 mg, or 21 per cent of the test dose, indicates disturbed function of the liver.

The results of the application of this test in various diseases and functional disturbances of the liver will next be presented

DISEASE OF THE GALLBLADDER AND BILE PASSAGES

The results tabulated in table 4 indicate that cases of acute and chronic inflammation of the gallbladder, with or without obstruction of the common duct due to stone or stricture, usually show relatively slight disturbance of the function of the liver, as manifested by figures above 100 and less than 200 mg, or from 21 to 42 per cent. The exceptions to the rule were the patient in case 3 (chronic cholecystitis and cholelithiasis) with a normal observation and the one in case 15 in which a man with a huge solitary stone of the common duct and slight fever showed excretions of 229 mg (47.5 per cent) and 304 mg (63 per cent). While the latter case gave no clinical indication of severe disturbance of the function of the liver, the icteric index was 50, and the bromsulphalein test showed 25 per cent retention in thirty minutes, thereby confirming the significance of the test.

The relief from biliary obstruction has a tendency to lower the figures. During the three to four weeks after operation that I have been able to follow up such cases, there usually has not been a return to normal. The presence or absence of fever does not seem to affect the results materially. The presence of cholangitis, at least of the larger bile ducts, does not appear to disturb this function of the liver cell to any great extent. Cases 6 and 10, in which there was fever up to 104 F, terminated fatally, and showed the presence of suppurative cholangitis post mortem, yet the test gave practically the same results as in other cases of disease of the common duct not complicated by suppuration.

CIRRHOSIS OF THE LIVER

Thirteen cases of cirrhosis of the liver due to various causes were studied (table 5). Three gave normal results (cases 20, 21 and 22). Case 18 was that of a woman in whom acute damage of the liver developed following an alcoholic spree. It is interesting that while

TABLE 4—Excretion of Oxy-Cinchophen in Disease of the Gallbladder and Bile Passages Test Dose of 0.45 Gm of Cinchophen, Rate of Excretion, Relation of Excretion to Body Weight and Temperature

Case	Weight, Kg	Temperature, F	Jaundice	Icterus Index	van den Bergh Reaction		Date of Test, 19-0	Excretion of Oxy Cinchophen in 12 Hr., Mg	Total Excretion of Oxy Cinchophen in 24 Hours		Diagnosis
					Direct	Quantitative, Mg			Mg	Per Cent	
1		101.0	0		Negative	0.5	2/12	27	171	35.5	Chronic cholecystitis, cholelithiasis (laparotomy)
2		100.0	0	8	Negative	0.2	1/21	0	138	28.5	Chronic cholecystitis, cholelithiasis
3			+				5/6	5	75	15.5	Chronic cholecystitis, cholelithiasis
4		100.2	0		Negative	1.0	5/10	20	127	26.5	Chronic cholecystitis, cholelithiasis
5	44.0 15.0	100.2 99.0	+	45	Negative	0.2	5/15 5/18	48 24	147 99	30.5 20.5	Chronic cholecystitis, cholelithiasis, choledocholithiasis
6		102.6 104.0	+	45 36	Positive Positive	1.5 2.0	4/27 5/11	8 54	175 106	36.5 22.0	Chronic cholecystitis, cholelithiasis, choledocholithiasis, cholangitis (necropsy)
7	72.0 73.0 73.0	98.6 98.6 98.6	+	20 18	Positive	0.5	6/7 6/10 6/15	0 38 53	153 155 165	33.0 32.5 34.5	Chronic cholecystitis, cholelithiasis, choledocholithiasis
8	50.0 50.5	99.8 99.2	+	18	Hemolyzed	0.2	5/13 5/17	40 63	130 163	27.0 34.0	Cholelithiasis, choledocholithiasis
9	77.0	99.4 99.4	+	65 30	Delayed Positive	0.9	5/30 6/2	99 27	170 97	35.5 20.0	Cholelithiasis, choledocholithiasis
10	43.0	103.0	+		Positive	0.9	2/13	40	167.4	31.5+	Cholecystitis, choledocholithiasis, purulent cholangitis, biliary fistula (necropsy)
11		100.0	+	50	Negative	1.0	1/30	19	113	23.5	Cholecystitis, cholelithiasis, stone of common duct
12		99.2	+		Negative	0.3	2/13	5	151	32.0	*Choledocholithiasis
13	60.0	99.8	+	20	Prompt positive	2.0	1/11	0	129	27.0	Choledocholithiasis, cholelithiasis
14	54.0	99.0	0	30	Negative	0.2	2/18	0	150	31.5	Stricture of common duct, duodenal fistula (laparotomy)
15	61.0 61.0	99.6 100.0	+	50	Delayed Positive	0.7	7/1 7/1	48 4	229 101	47.5 63.0	Stone of common duct (laparotomy)
16	61.0 61.0	99.2 99.4	+	56 15	Positive Positive	1.5 0.5	6/16 6/10	26 0	151 168	32.0 55.0	Acute cholecystitis, cholangitis, "infectious jaundice"

TABLE 5—*Cirrhosis of the Liver*

Case	Weight, Kg	Tempera- ture, F	White Blood Cells	Jaun- dice	Icterus Index	van den Bergh Reaction		Retention of Brom- sulphalein, per Cent in 30 Minutes	Date of Test	Excretion of Oxy- cincho- phen in Second 12 Hr., Mg	Total Excretion of Oxy Cinchophen in 24 Hours		Diagnosis
						Direct	Quant- itative, Mg				Mg	Per Cent	
17	58.5 57.5 57.5	100.2 100.0 100.8	9,100	+	10 15 15	Delayed Positive	1.2	45	1/19 2/7 2/20	50 98 45	300 349 113	62.5 73.0 25.0	Biliary cirrhosis (biopsy)
18	56.5 56.5 55.0	100.6 99.2 99.8	5,900	+	30 + Slight	Delayed Positive	1.0		2/6 2/9 2/16	30 ? 0	106+ 223+ 332	22.0+ 46.5+ 69.0	Alcoholic cirrhosis
19	95.0	99.6	8,000	0	10	Negative	0.2	5	4/29	0	204	42.5	Alcoholic cirrhosis
20	55.5 55.5	98.8 100.0	11,200	0	30 8	Delayed Positive	1.2	35 0	2/28 3/4	13 26	91 73	19.0 15.0	Alcoholic cirrhosis
21	41.0	99.6		0					2/27	9	65	13.5	Syphilitic cirrhosis (portal), laparotomy
22	56.0	98.6	10,400	0	8	Negative	0.2	5	3/6	0	74	15.5	Cirrhosis, splenic thrombosis
23	66.0	99.2	8,800	0	15	Delayed positive	0.6	20	2/25	16	109	22.5	Cirrhosis (portal, Laennec), ascites (necropsy)
24	50.0 49.5 49.5 50.0 50.0	99.2 99.8 99.4 99.0 99.1	9,200	+	125 75 + (receding) + 120	Prompt Positive	3.0	50	5/27 5/29 6/1 6/6 6/14	0 66 0 150 88	185 106 66 315 164	38.5 22.0 14.0 65.6 34.0	Syphilitic cirrhosis
25	52.0 53.0 53.0	99.0 99.6 99.0	6,100	+	125 40 0	Positive Delayed Positive	5.5 0.3		2/14 2/16 2/23	24 0 0	250 116 60	52.0 24.0 12.5	Syphilitic cirrhosis
26	65.0	99.6	5,530	+	30	Negative	1.0	5	5/3	15	142	29.5	Hepatosplenomegaly, hyperthyroidism
27	75.5 75.0	99.8 99.4	5,600	0	12	Negative	0.5	20	6/8 6/11	44 25	143 100	30.0 21.0	Splenomegalic cirrhosis, anemia (necropsy)
28	52.0 52.0	99.4 99.4	2,900	0	10	Negative	0.2	5	5/3 6/7	8 0	260 143	54.0 30.0	Hematosplenomegaly (schistosomiasis)
29	57.0 57.0	99.6 99.2	5,360	0		Delayed Positive	0.8		5/29 6/1	23 54	137 190	28.5 39.5	Hematosplenomegaly (melanosis)

the jaundice was receding and the patient was apparently improving clinically, successive tests showed increasing disturbance of the function of the liver. Case 17 illustrates the value of the test in following the course of pathologic changes. The patient had a huge liver which on biopsy showed hypertrophic biliary cirrhosis. Under observation the liver rapidly diminished in size until it was felt just below the costal margin. The successive observations showed a rapid fall in excretion from 300 and 349 mg (62.5 and 73 per cent) to 113 mg (23.5 per cent).

Results above 200 mg (42 per cent) of excretion in cases of cirrhosis of the liver seem to signify the presence of acute degenerative changes, those between 150 mg (31.5 per cent) and 200 mg (42 per cent) suggests mild or receding degenerative changes. Normal results and figures below 150 mg (31.5 per cent) were obtained in cases that were clinically "quiescent."

No parallelism was noted between the quantitative results of the van den Bergh test, the icteric index, the Rosenthal bromsulphalein test and the test with oxy-cinchophen in this group of cases. The reason for this probably lies in the fact that the first three tests are influenced by biliary obstruction, whereas the test with oxy-cinchophen is influenced only by parenchymal disease or other factors that disturb the function of the hepatic cells.

CATARRHIAL JAUNDICE

The group comprises four cases of painless jaundice occurring in patients with no antecedent history indicative of disease of the liver or of the gallbladder, with and without fever and accompanied by gastro-intestinal disturbances such as vomiting and diarrhea (table 6). The results were the upper limit of normal or low abnormal figures, well below 200 mg (42 per cent), such as are usually found in cholelithiasis and choledocholithiasis.

A significant observation is the sudden temporary increase in the excretion of oxy-cinchophen observed in cases 31 and 32, suggesting transitory damage of the liver and a rapid reparative process. An absolutely normal level was not reached, even when complete clinical recovery had apparently taken place. Case 30 showed the presence of tyrosine in the urine in a single examination by the tyrosinase method.²¹

In case 33 studied prior to a complete remission of the jaundice, the figures were only slightly elevated. Two months later jaundice recurred, and the patient died. Necropsy revealed subacute yellow

21 Lichtman, S. S., and Sobotka, H. An Enzymatic Method for the Detection and Estimation of Tyrosine in Urine, *J. Biol. Chem.* 85: 261 (Dec.) 1929.

TABLE 6—*Catarrhal Jaundice*

Case	Weight, Kg	Tempera- ture, F	White Blood Cells	Jaun- dice	Icterus Index	van den Bergh Reaction		Retention of Brom- sulphalein, in 30 Minutes	Date of Test	Excretion of Oxy- cincho- phen in Second 12 Hr., Mg	Total Excretion of Oxy Cincho- phen in 24 Hours		Diagnosis
						Direct	Quant- itative, Mg				Mg	Per Cent	
30	72.5	101.4	17,800	+	30	Negative	1.5	100	11/23/29	?	203+	42.0+	Catarrhal jaundice
31	63.5	98.6	5,100	+		Prompt, positive	0.3		2/4	6	113	23.5	Catarrhal jaundice
	60.0	99.0		0		Delayed, positive	0.2		2/7	37	243	51.0	
	66.0	99.0		0					2/10	0	95	20.0	
32	59.0	99.2	7,500	+	70	Negative	0.5	60	4/8	0	96	50.0	Catarrhal jaundice
	63.0	99.0		+	120	Prompt, positive	9.0		4/12	0	109	22.5	
	59.5	99.2		+	75	Delayed, positive	0.3		4/18	0	204	42.5	
	61.5	99.2		+	75	Delayed, positive	0.3		4/23	0	84	17.5	
	61.5	99.0		0	20	Delayed, positive	0.2		4/29	127	357	74.0	
	63.0	99.0		0	30	Delayed, positive	0.3		5/11	48	149	31.0	
33	66.5	99.0		0					5/18	30	153	32.0	Catarrhal jaundice (necropsy)
	79.0	99.4	7,000	+	170	Delayed, positive	1.5		5/9	48	118	24.5	
	80.0	100.8		+	70 45	Delayed, positive	1.5		5/17	33	106	22.0	

atrophy of the liver Unfortunately, because of vomiting a satisfactory test was not made in the patient's second admission to the hospital

Although the figures for the excretion of oxy-cinchophen in catarrhal jaundice are often only slightly above normal, the transitory character of the rise at one stage of the disease in two of the cases suggested the presence of true parenchymal degeneration, from which recovery was apparently rapid The occurrence of pathologic changes of this nature in cases that are clinical examples of catarrhal jaundice has already been recognized ²²

"TOXIC HEPATITIS", HEPATOSIS, CHRONIC HEPATITIS,
"CHOLANGEITIS LENTA"

In this group are included eight cases of diffuse inflammatory or degenerative disease of the liver, with or without jaundice, sometimes associated with fever and chills and with or without enlargement of the liver In some cases the condition is referred to as acute or chronic hepatitis One is a case of so-called "cholangitis lenta," in which there proved to be an inflammatory process involving the periportal fields in the vicinity of the bile ducts Others are cases of "toxic hepatitis" or hepatosis due to intoxications with arsenicals, phenyl-cinchoninic acid or phenyl-ethyl barbituric acid, etc (table 7)

Case 35 is an unusual instance of icterus due to degeneration of the liver that followed repeated therapeutic intravenous infusions of hypertonic salt solution (thrombo-angitis obliterans) This case was studied in the convalescent stage and even then showed an excretion of 302 mg, or 63 per cent, with a rapid decline to 37 per cent in one week coincidental with improvement Case 34 is an instance of icterus following the ingestion of approximately 18 Gm of cinchophen over a period of eighteen days This case showed evidence of the greatest amount of disturbance of hepatic function in the entire series (375 mg, or 78 per cent) Case 39 was that of a man with lobar pneumonia with toxic jaundice following the crisis In this case the result of the test indicated definite damage of the liver (236 mg, or 49 per cent)

Case 41 is one of "cholangitis lenta," diagnosed by biopsy, showing leukocytic infiltration of the periportal fields, especially around the bile ducts, thickening of the stroma and the retention of bile within the hepatic cells, with no evidence of cirrhosis The excretion was 233 mg (48.5 per cent), 218 mg (45.5 per cent) and 226 mg (47 per cent) respectively, on three tests made over a period of a week

²² Klemperer P Killian, N A, and Heyd, C G The Pathology of "Icterus Catarrhalis," Arch Path 2 631 (Nov) 1926

TABLE 7 — "Toxic Hepatitis" or Hepatosis, Chronic Hepatitis, "Cholangietis Lenta"

Case	Weight, Kg	Tempera- ture, F	White Blood Cells	Jaun- dice	Icterus Index	van den Bergh Reaction		Retention of Brom- sulphalein, in 30 Minutes	Date of Test	Excretion of Oxy- cincho- phen in Second 12 Hr., Mg	Total Excretion of Oxy Cinchophen in 24 Hours		Diagnosis
						Direct	Quantita- tive, Mg				Mg	Per Cent	
34	58.0	103.2	7,100	+	100	Prompt, positive	8.0		5/9	72	375	78.0	Toxic hepatosis (cinchophen)
	58.0	103.0		+	150		2.0		5/15	157	353	73.5	
	58.0	103.6		+	100		2.0	50	5/25	10	141	29.5	
35	67.5	99.0		+	25	Negative	0.2	35	2/7	53	302	63.0	Hepatosis (hypertonic saline) infusion
	68.0	99.0		Slight					2/14	83	177	37.0	
36	37.0	100.2	11,800	+	75	Prompt, positive	3.4	5	4/3	0	125	26.0	Toxic hepatosis (phenobarbital), in solu- tion
	35.0	99.0		+	35	Negative			4/12	11	226	47.0	
	36.5	100.2		0	15				4/23	0	137	28.5	
37	62.0	98.6		0					2/14	12	169	37.5	Arsenical "hepatitis" (convalescent)
	60.0	98.6		0					2/23	25	117	25.0	
38	42.5	99.4	9,100	0		Prompt, positive	3.0	80	2/4	128	307	64.0	Chronic hepatitis, cholangietis?
	42.5	101.2		0	30				2/7	0	111	23.0	
	41.0	99.0		0					2/10	120	198	41.0	
	40.0	99.4		0	25	Delayed, positive	1.0	55	2/16	23	158	33.0	
39	53.0	99.0	14,500	0					4/3	90	236	49.0	Toxic hepatitis (lobar pneumonia)
				Previously									
40	39.5	99.2	18,000	+	30	Negative	0.2	35	2/13	34	176	36.5	Chronic hepatitis
	39.5	99.4		+					2/17	2	191+	40.0	
	38.5	99.8		+	25	Negative	0.3	5	2/23	44	207	43.0	
	35.0	99.4		+	18				3/15	0	194	40.5	
41	57.0	99.6	11,300	+	70	Delayed, positive	2.6		7/1	63	233	48.5	"Cholangietis lenta"
		99.8		+					7/3	50	218	45.5	
		99.8		+					7/5	23	226	47.0	

In this group of cases of diffuse disease of the liver, results above 200 mg (42 per cent) were usually obtained. In the more severe cases with diffuse parenchymal degeneration, readings above 300 mg (63 per cent) were observed.

CARCINOMA OF THE LIVER

One case of primary endocellular carcinoma of the liver and seven cases of metastatic carcinoma of the liver were studied (table 8).

The primary tumor of the liver diagnosed by biopsy occurred in a boy, aged 18 (case 42). The initial test showed an excretion of 295 mg (61.5 per cent) with a corresponding retention of bromsulphalein of 50 per cent and a low icteric index of 20. During the succeeding three months, during which the patient received a course of radiotherapy, unfortunately he was not observed. The test now repeated showed a marked decline in the excretion of oxy-cinchophen to 108 mg (22.5 per cent) or slightly above normal with a corresponding decrease in the retention of bromsulphalein to as low as 5 per cent in thirty minutes. The general condition of the patient remained unchanged, but the slight jaundice almost disappeared in the interval between the tests.

In the cases of metastatic carcinoma, regardless of their origin, the test gave results well below 200 mg. At necropsy in case 43, it was observed that the right lobe of the liver was replaced by a huge circular solid metastasis from a primary carcinoma of the hepatic flexure of the colon, the remaining part of liver appeared normal. The result in this case was 133 mg (27.5 per cent).

It is noteworthy that tests repeated at short intervals may show a decline in the excretion of oxy-cinchophen, suggesting improved and even normal function. The cholorectic action of the test dose may possibly account for the apparent improvement in the function of the liver.

CARCINOMA OF THE PAPILLA OF VATER

Two cases of carcinoma of the papilla of Vater were studied (table 9). Case 48, confirmed by biopsy, was studied thirteen months following the resection of an adenocarcinoma of the papilla of Vater. Tests made before and after the establishment of drainage by secondary choledochostomy showed excretions of 294 mg (61 per cent) and 265+mg (55+per cent), respectively, the latter figure being incomplete, owing to leakage of bile through surgical dressings. The necropsy in this case showed degeneration of the liver.

In case 49 the diagnosis is not conclusive, as it rested on a palpatory laparotomy observation. With only slight disturbance of the function of the liver, an excretion of 144 mg (30 per cent) and 122 mg (25.5

TABLE 8—*Carcinoma of the Liver*

Case	Weight, kg	Tempera- ture, F	White Blood Cells	Jaun- dice	Icterus Index	van den Bergh Reaction			Retention of Brom- sulphalein, per Cent in 30 Minutes	Date of Test	Excretion of Oxy- cineho- phen in Second 12 Hr., Mg	Total Excretion of Oxy Cineho- phen in 24 Hours		Diagnosis
						Direct	Hemolyzed	Quantitative, Mg				Mg	Per Cent	
42	49.0 49.2	100.2 100.2	10,200 9,800	+	20 15		Hemolyzed Prompt, positive	0.2 1.0	50 5	3/28 6/6	41 51	295 198	61.5 22.5	Primary carcinoma of liver (biopsy), radiotherapy
43		99.4		0	5				10	2/20	78	133	27.5	Colloid carcinoma of hepatic flexure of colon, metastasis to liver (necropsy) Metastatic carcinoma of liver (biopsy)
44	42.0 43.5	100.0 99.0	5,800	0 0	5				0	3/25 3/28	15 15	154 186	32.0 38.5	
45	48.0 47.5	99.2 99.1		0 0	6				15	2/26 3/8	30 22	63 149	13.0 31.0	Carcinoma of prostate, metastasis to liver
46	61.0 61.0	99.6 99.0		0 0						1/24 1/28	11 0	138 98	28.5 20.5	Carcinoma of liver, abdominal carci- noma, ascites
47	45.0	102.2	10,800	0	6	Negative		0.2		5/19	36	118	24.5	Carcinoma of stomach, metastasis to liver

TABLE 9—*Carcinoma of Papilla of Vater and of Pancreas*

Case	Weight, Kg	Tempera- ture, F	White Blood Cells	Jaun- dice	Icterus Index	van den Bergh Reaction		Retention of Brom- sulphalein, per Cent in 30 Minutes	Date of Test	Excretion of Oxy- cincho- phen in Second 12 Hr., Mg	Total Excretion of Oxy Cinchophen in 24 Hours		Diagnosis
						Direct	Quant- itative, Mg				Mg	Per Cent	
38	57.5 48.0	99.0 99.6	5,500	0	35 16	Negative	0.2		2/7 4/1	90 60	294 265	61.0 55.0	Adenocarcinoma of papilla of Vater resec- tion, biliary fistula, cholangitis, de- generation of the liver (necropsy)
49	58.0 58.0 58.0 57.5 56.0	98.6 100.2 100.0 101.2 99.4	6,200	+	150	Prompt, positive	7.0		5/21 5/23 5/25 6/1 6/10	60 28 29 59 50	144 122 257 326 193	30.0 25.5 53.5 68.0 27.5	Carcinoma of papilla of Vater (laparot- omy) biliary fistula
50		100.8		+		Prompt, positive	6.0		4/3	117	311	65.0	Carcinoma of head of pancreas (clinical)
51		99.8	8,100	+		Prompt, positive	7.0		2/18	50	219	45.5	Carcinoma of head of pancreas (clinical)
52	38.5	98.0	10,400	+	25	Delayed, positive	0.9	50	4/2	30	217	51.0	Carcinoma of body and tail of pancreas (necropsy)
53		100.1	16,400	+	125	Prompt, positive	3.0		1/22	135	367	76.5	Carcinoma of head of pancreas (clinical)
54		99.6 99.8	13,200	+	100	Prompt, positive	4.4	80	3/21 3/23	0 0	288 256	60.0 53.0	Carcinoma of head of pancreas (laparot- omy)

per cent) at the outset, the excretion increased rapidly in the course of a week up to 326 mg (68 per cent). Nine days after relief from the obstruction by choledochostomy performed under local anesthesia, the excretion was 133 mg (27.5 per cent), the result being incomplete owing to leakage of bile through the dressings. The amount of oxy-cinchophen and cinchophen thus lost may have been considerable, it is difficult to estimate.

CARCINOMA OF THE PANCREAS

Five cases of carcinoma of the pancreas were studied (table 9). In one, the diagnosis was confirmed by necropsy (case 52), in a second by laparotomy (case 54) and in the remaining three, the diagnosis was clinical. In the first case the body and tail of the pancreas were involved, and the diagnosis was made before the appearance of jaundice, due to the presence of hyperglycemia, and roentgen evidence of chronic duodenal stasis caused by carcinomatous involvement of the duodeno-jejunal angle. Jaundice, which varied in intensity, was due to involvement of the lymph nodes of the porta hepatis and numerous small metastases in the liver. A single test revealed an excretion of 247 mg (51 per cent) of oxy-cinchophen. The remaining four cases, 50, 51, 53 and 54 (case 54 was confirmed by laparotomy) were diagnosed as involving the head of the pancreas. Except for case 51, which is incomplete due to loss of some urine with the stool, the readings varied between 247 mg (51 per cent) and 367 mg (76.5 per cent).

The elevation in excretion of oxy-cinchophen above 200 mg may be present even before the appearance of jaundice. The explanation of this degree of disturbance in hepatic function in carcinoma of the pancreas awaits further investigation. Whether the chronic partial obstruction of the common duct, the chemical changes in the duodenum due to the diminution or exclusion of pancreatic secretion, disturbance in the function of glycogen storage by the liver or actual pathologic changes in the liver, as have been observed in dogs following pancreatectomy,²³ play a rôle is at present a matter for conjecture.

Should these results be maintained in a larger series of cases, this test might aid in the differentiating jaundice due to stone in the common duct from that due to carcinoma of the pancreas.

HEPATIC DYSFUNCTION IN EXTRAHEPATIC DISEASE

This group comprises forty-seven cases (table 10), cases of duodenal ulcers, acute rheumatic fever, exophthalmic goiter, pulmonary disease,

²³ Allan, F. N., Bowie, J. D., Macleod, J. J. R., and Robinson, W. L. Behavior of Depancreatized Dogs Kept Alive with Insulin, *Brit J Exper Path* 5: 75, 1924.

TABLE 10—*Extrahepatic Diseases with Increased Excretion of Oxy-Cinchophen*

Case	Weight, Kg	Tem- pera- ture, F	Date of Test	Excretion of Oxy Cincho- phen in Second	Total Excretion of Oxy Cinchophen in 24 Hours		Diagnosis
				12 Hr., Mg	Mg	Per Cent	
55	62.0	98.6	1/16	0	119	25.0	Duodenal ulcer
	63.0	99.0	2/3	0	102	21.0	
	60.0	99.4	2/15	38	153	32.0	
56	58.5	99.0	1/15	40	138	28.5	Duodenal ulcer, syphilis
57	58.0	99.0	5/1	32	110	23.0	Duodenal ulcer, syphilis
	58.0	99.0	5/3	18	102	21.0	
58	60.5	99.6	1/29	0	95	20.0	Acute rheumatic fever
	62.0	99.8	2/8	41	276	57.5	
	63.0	99.0	2/22	17	136	28.5	
59	72.0	99.2	1/27	74	167	35.0	Acute rheumatic fever (mitral and aortic disease)
	71.5	99.2	2/1	16	129	27.0	
	72.0	99.4	2/8	16	133	27.5	
60	59.0	98.6	2/25	38	181	37.5	Acute rheumatic fever (mitral and aortic disease)
61	55.0	99.4	1/14	63	120	26.0	Acute rheumatic fever
62		101.0	3/27	41	164	34.0	Lobar pneumonia, duodenal ulcer
63	57.0	98.6	1/20	0	212	44.0	Lobar pneumonia, duodenal ulcer
	57.0	98.6	1/25	5	119	25.0	
64	61.5	99.6	3/4	65	116	24.0	Lobar pneumonia, duodenal ulcer
	61.5	99.6	3/6	77	141	29.5	
65	41.0	99.0	4/16	0	104	21.5	Lobar pneumonia, duodenal ulcer
66	55.0	99.8	2/23	0	84	17.5	Bronchopneumonia, (interval of fever 100.4 F prior to second test)
							Bronchopneumonia
67	68.0	99.0	4/30	38	216	45.0	
	68.5	99.0	5/2	0	153	32.0	
68	64.0	99.8	3/19	37	174	36.0	Bronchopneumonia, mucous colitis
	62.5	99.0	4/1	0	113	23.5	
69	88.0	99.8	1/25	19	162	34.0	Bronchopneumonia, bronchiectasis
	87.0	100.0	2/1	23	139	29.0	
	88.0	99.8	3/1	13	75	15.5	
	88.0	99.6	3/7	0	81	17.0	
70	70.5	99.2	2/20	39	120	25.0	Bronchiectasis
	70.5	99.0	6/1	51	150	31.0	
71	58.5	99.0	1/18	3	185	38.5	Pulmonary tuberculosis
	63.0	99.2	1/27	0	85	17.5	
	64.0	98.6	2/5	45	142	29.5	
72	58.5	98.6	2/19	95	305	63.5	Pleurisy with effusion
	58.5	98.6	2/25	0	74	15.5	Tuberculosis
73	52.0	99.4	1/30	30	155	32.5	Miliary tuberculosis (pulmonary), migraine
74	31.5	101.4	2/22	0	147	30.5	Tuberculosis of mediastinal lymph nodes
75	45.0	100.4	2/25	12	109	22.5	Neoplasm of left lung
76	65.0	99.2	2/27	30	119	25.0	Mitral stenosis and insufficiency
77	45.5	99.2	1/24	25	114	23.5	Chronic cardiovascular disease, mitral, aortic disease, auricular fibrillation, hydrothorax
78	63.0	99.0	1/17	38	107	22.5	Chronic cardiovascular disease, mitral, tricuspid disease, hydrothorax, ascites
79	55.0	99.0	1/21	40	117	24.5	Chronic cardiovascular disease mitral, aortic disease, splenomegaly
80	60.0	103.8	1/15	0	153	32.0	Subacute bacterial endocarditis
	60.0	104.2	1/21	0	158	33.0	Aortic insufficiency
81	57.0	102.4	1/23	23	126	26.0	Subacute bacterial endocarditis (healed) lupus erythematosus
82	65.0	99.0	2/14	75	162	33.5	Mitral stenosis and insufficiency
	65.0	100.8	2/22	64	176	36.5	Hepatosplenomegaly
83	44.0	99.2	2/8	18	134	28.0	Polycythemia vera
84	55.0	98.6	1/19	0	242	50.0	Polycythemia, splenomegaly
	55.0	98.6	2/17	36	131	27.5	
85	70.0	98.6	2/2	14	68	14.0	Polycythemia, hepatosplenomegaly
86	67.5	99.6	2/20	28	128	26.5	Hypertension, exophthalmic goiter
87	45.0	99.0	5/10	30	126	26.0	Hypertension
88	47.0	99.2	5/8	45	204	42.5	Exophthalmic goiter
89	87.5	98.4	2/14	8	146	30.5	Exophthalmic goiter
90	65.0	99.8	3/11	?	158	33.0	Left sciatic neuritis
91	61.0	99.4	2/26	8	174	36.0	Bronchial asthma
	60.0	98.8	3/8	32	111	23.0	
92	43.0	97.8	3/11	?	139	29.0	Subsiding tonsillitis
93	?	?	2/18	0	108	22.5	Multiple carcinomas of the bone (biopsy)

TABLE 10—*Extrahepatic Diseases with Increased Excretion of Oxy-Cinchophen*
—Continued

Case	Weight, kg	Tem- pera- ture, F	Date of Test	Excretion of Oxy Cincho- phen in Second 12 Hr ,	Total Excretion of Oxy Cinchophen in 24 Hours		Diagnosis
				Mg	Mg	Per Cent	
94	52.0	99.4	2/18	0	128	26.5	Multiple carcinomas of the bone (biopsy)
95	48.0	102.0	2/20	45	150	31.0	Chronic lymphatic leukemia, Hodg- kin's disease (necropsy)
96	50.0	100.4	4/30	53	150	31.0	Erythema multiforme
	53.5	99.4	5/ 2	105	178	37.0	
97	67.0	98.6	4/16	0	155	32.5	Pararectal disease, myocardial insufficiency
98	65.0	99.0	2/ 3	0	49	10.5	Penetrating gastric ulcer (roentgen examination)
	65.0	99.0	2/ 6	0	104	21.5	
99	57.0	101.0	1/28	46	110	23.0	Miliary carcinosis of lung
100	57.0	99.4	1/18	45	206	43.0	Ulcerocarcinoma of stomach, bron- chopneumonia (necropsy)

chronic heart failure and a miscellaneous group are included. Cases of this type may show normal readings. In those with abnormal readings, the excretion of oxy-cinchophen is as a rule less than 200 mg (42 per cent). Exceptionally, isolated readings as high as 300 mg (63 per cent) occur in pneumonia, pleurisy with effusion and tuberculosis. The absence of frank jaundice in these cases indicates that moderate or even severe disturbance may occur in the metabolic functions of the liver without material disturbance in the excretion of bile.

COMMENT

A relatively constant excretion of oxy-cinchophen in the urine occurs with repeated test doses of cinchophen (0.45 Gm.) in the same normal subject. In patients with hepatic dysfunction, a higher excretion of oxy-cinchophen follows the ingestion of the test dose. Under uniform conditions in the same patient, this excretion is also constant. After a larger dose (0.9 Gm.), however, the patient with hepatic dysfunction excretes a variable, sometimes lower, sometimes higher, percentage of the dose as oxy-cinchophen.

If a small dose (0.1 Gm.) of oxy-cinchophen is fed to persons with normal and to those with abnormal function of the liver, only a fraction of it reappears in the urine, approximately the same amount as when an equal dose (0.1 Gm.) of cinchophen had been administered.

The clinical observations indicate a certain parallelism between the total excretion of oxy-cinchophen and the degree of damage to the liver. The following theoretical basis for these observations is suggested. The constant excretion of oxy-cinchophen following repeated test doses of 0.45 Gm., given orally, and also the larger dose (0.9 Gm.) of cinchophen in the same normal subject depends on a uniform rate of absorption and a constant metabolic rate for cinchophen in the liver. With these doses a relatively constant amount of cinchophen is con-

verted to oxy-cinchophen and the remainder disposed of in some other manner (excreted as cinchophen, oxypyridinuric acid,¹⁹ etc.) With a larger dose of cinchophen (0.9 Gm.), the abnormal liver cannot maintain this constant metabolic rate, larger fractions of the ingested dose fail to be metabolized beyond the stage of oxy-cinchophen, and therefore larger amounts of this oxidation product appear in the urine.

Thus oxy-cinchophen probably represents an intermediary product in the destruction of cinchophen by the liver. The abnormal cells of the liver convert cinchophen to oxy-cinchophen, but the subsequent catabolism of this substance proceeds at a slower rate and to a lesser degree. With increasing disturbance of the function of the cells of the liver, larger and larger fractions of the standard dose are consequently eliminated in the urine as oxy-cinchophen.

It has been contended that because of the manifold functions of the liver and the great reserve of liver tissue, a test of any single function cannot be used as an index of function of the organ as a whole. My test, however, depends on a metabolic function of the liver that apparently is among the first to be disturbed and moreover is apparently disturbed in proportion to the extent and severity of the disease. Therefore, I believe that it offers the possibility of a quantitative index of the extent of damage or dysfunction of the cells of the liver.

The present test is not to be considered a tolerance test for cinchophen, since the excretion of one of its metabolic conversion products, and not of the unaltered substance, is measured.

The interpretation of the results of the test is based on a series of approximately fifty cases of disease of the liver and the gallbladder and fifty of nonhepatic disease in which evidence of hepatic dysfunction was obtained. The diagnostic possibilities of the test as indicated in the discussion of the different groups of cases must be further applied in a larger series of carefully studied cases to determine its clinical value.

SUMMARY

A practical, simple and extremely sensitive colorimetric method for the estimation of 2-(ortho-hydroxy-phenyl)-quinoline-4-carboxylic acid (oxy-cinchophen) is described, based on the characteristic Skorczewski-Sohn color reaction and revealing this substance in dilutions of 0.0002 per cent.

This test for the function of the liver is based on the estimation of the twenty-four hour excretion of oxy-cinchophen in the urine following the ingestion of a standard dose of 0.45 Gm. of cinchophen. In a group of fifty subjects without hepatic dysfunction, from 30 to 100

mg, or from 7 to 21 per cent, of the test dose, was excreted as oxy-cinchophen

The increase in excretion of oxy-cinchophen in the urine may be useful as a quantitative index of an altered metabolism of the cells of the liver whereby they have lost their capacity to decompose this substance further

Biliary stasis or obstruction per se does not materially influence the results of the test, at least not early in the disease

The ingestion of a standard test dose of 0.45 Gm of cinchophen has not elicited any hepatotoxic effects

A limited clinical experience with the test suggests certain diagnostic opportunities. The results indicate that in biliary obstruction due to stone or stricture and in metastatic carcinoma of the liver the daily excretion of oxy-cinchophen is usually less than 200 mg (42 per cent), while in diffuse degenerative and acute inflammatory lesions involving the parenchyma of the liver more than 200 mg is excreted in twenty-four hours. In cirrhosis of the liver the results may be normal or below 200 mg in the chronic stage and above 200 mg only when an acute or subacute degeneration of the liver is superimposed. In catarrhal jaundice the results are usually below 200 mg with an occasional sharp increase on repeated tests. In carcinoma of the pancreas a persistent increase above 200 mg has thus far been obtained.

In extrahepatic diseases, such as chronic heart failure, duodenal ulcer, exophthalmic goiter, acute rheumatic fever and pneumonia, there is sometimes an increase in the excretion of oxy-cinchophen.

PHYSOSTIGMINE SALICYLATE IN THE TREATMENT OF EXOPHTHALMIC GOITER

OBSERVATIONS ON TWO HUNDRED CASES [†]

ISRAEL BRAM, M D

PHILADELPHIA

It can safely be assumed that irrespective of the form of treatment advocated or adopted for sufferers from exophthalmic goiter, the uppermost immediate aim of the physician is a reduction of the heart rate to normal. Many clinical facts justify this aim. The heart bears the brunt of the damage wrought by the intensity and duration of exophthalmic goiter, and cardiac failure is the usual cause of death. The height of the heart rate and the output of blood usually parallel the severity of the other manifestations of the disease, likewise, amelioration of symptoms or recovery of the patient is announced by a calming of the heart rate and force. Indeed, so constantly is a significant behavior of the heart associated with the varying phases of this syndrome that the heart's action may be regarded as a most reliable criterion of the course of the disease during crisis, remission or recovery as the case may be ¹

DIGITALIS IN TREATMENT

The tachycardia of exophthalmic goiter is characterized by features that in combination assist considerably in its diagnosis. These are (*a*) its afebrile character, (*b*) its association with a high basal metabolic rate, (*c*) its chronicity, being weeks, months or years in duration, (*d*) its constancy, being but little altered by rest or sleep, and (*e*) its resistance to the influence of digitalis even in large doses.

Personal (unpublished) observations conducted on a series of 100 cases ten years ago revealed that digitalis may be of benefit in exophthalmic goiter in approximately 50 per cent of the cases only under the following conditions: (1) in combination with quinidine sulphate in efforts at restoration of rhythm in a fibrillating heart, (2) during approaching or actual remission, (3) during impending or actual circulatory decompensation, and (4) when in the favorable course of the disease improvement in the condition of the heart lags behind obvious

[†] Submitted for publication, Nov 19, 1930

¹ This exception must be noted. In spontaneous or induced myxedema complicating or modifying the disease, the heart rate may be normal or below without recovery of the patient, since circulatory calm may mask a residual or potentially active Graves' syndrome.

improvement elsewhere, in other words, when under successful treatment, the basal metabolic rate, weight, sense of well-being and other clinical evidences point to impending recovery, but the heart rate, probably from force of habit of the tissues, is still 80 or over, the administration of digitalis may succeed in its purpose. In those observations we sought to evaluate the effects of digitalis on the tachycardia of active, previously untreated cases of exophthalmic goiter and found the drug practically valueless as far as the heart rate was concerned. In 10 of the series of 100 patients the dose of the standard tincture of digitalis was increased to 1 drachm three times a day for a period of three weeks with no discernible lowering of the heart rate. Indeed, in 3 of these patients, there resulted an increase in the heart's excitability. In 5 of the 10 patients, the dosage was increased to 2 drachms three times a day for an added week. This aggravated the entire syndrome. It appears that the drug created a sort of vicious circle, namely, it engendered digestive disturbances and an aggravation of the syndrome, and this in turn increased the heart's rate.

These comments are applicable also to the various derivatives of digitalis and to the commonly employed "heart stimulants," including strophanthus, convallaria root and sparteine. Our observations of a decade ago included the use of practically all of the popular drugs for the action of the heart, and the conclusion drawn was that as far as the tachycardia of active exophthalmic goiter was concerned, the use of these substances was without tangible benefit.

It is evident that success in the treatment of tachycardia in exophthalmic goiter may be expected only when measures are directed toward the cause of cardiac excitability. Whether this rests primarily in an excess of thyroid hormone in the blood is still a moot question related to the controversial problem of whether exophthalmic goiter and toxic adenoma are different manifestations of the same disease. With regard to the direct or immediate cause of excessive cardiac activity, the consensus points to an overactivity of the cardiac accelerator nerves issuing from the sympathetic nervous system. The tachycardia appears to be the result of a dominating sympatheticotonia, over which the checking influence of the vagus nerve is insufficient to maintain a normal heart rate.

It is, therefore, reasonable to assume that any measure capable of alleviating sympatheticotonia either directly or by stimulation of the vagus nerve or both could rightly claim an important place in the treatment of exophthalmic goiter. Also it appears reasonable to infer that such a measure could favorably influence other sympatheticotonic evidences as exophthalmos and the intestinal sluggishness observed in a percentage of cases.

PHYSOSTIGMINE SALICYLATE VERSUS SYMPATHETICOTONIA

Our observations during a period of one year (ending June, 1930) in a series of 200 cases of active exophthalmic goiter indicate that physostigmine is a remedy largely conforming with the requirements mentioned. While the literature on the subject is rather meager, yet occasional mention is made of the benefit derived from the administration of this drug in cases of tachycardia with and without involvement of the thyroid. Among the contributors are Mougeot,² Lian and Welti,³ Moutier,⁴ de Meyer,⁵ and Plitman and Ender.⁶

According to Cohen and Githens,⁷ physostigmine exerts its action chiefly on the autonomic nervous system, slowing the heart by a stimulating influence on the cardiac endings of the vagus nerve. There is also evidence to indicate that physostigmine exerts a depressing effect on the cardiac accelerator fibers issuing from the sympathetic nervous system. In our series of observations, physostigmine reduced the force and rate of the heart's action in approximately 73 per cent of the cases, with resultant improvement in subjective and objective symptoms. Moreover, this drug exerts a beneficial influence on exophthalmos and overcomes defective intestinal elimination. So valuable a substance did we find physostigmine to be that it is felt that its use should become widespread as an important constituent in the armamentarium of all clinicians who have patients of this sort under their care. Theoretically, it would appear that a reduction of heart rate and force would reduce the vascularity and size of the thyroid gland and consequently the excitability of this organ. This actually occurred in quite a few cases in this series.

CLINICAL FEATURES IN THE TWO HUNDRED CASES OF EXOPHTHALMIC GOITER IN WHICH PHYSOSTIGMINE SALICYLATE WAS EMPLOYED

The age of the patients ranged from 7 to 64 years, with an average of 31 years. There were 142 females, or 71 per cent, and 58 males, or 29 per cent. The duration of the illness, as stated by the patients

2 Mougeot, J. Physostigmine Test in Cardiology, *Bull et mém Soc méd d hôp de Paris* **45** 512, 1921.

3 Lian, C, and Welti, H. Treatment of Tachycardia, *Bull et mem Soc méd d hôp de Paris* **45** 559, 1921.

4 Moutier, F. Eserine in Internal Therapeutics, *Paris med* **11** 453, 1921.

5 de Meyer, J. Intermittent Acceleration of Sinus Rhythm, *Arch d mal du coeur* **15** 265, 1922.

6 Plitman, M, and Ender, S. Reinforcement of Physostigmine by Serum Through Action of Thyroid, *Ztschr f d ges exper Med* **57** 361, 1927.

7 Cohen, S S, and Githens, T S. Pharmacotherapeutics, New York, D Appleton & Company, 1928, p 1780 and 1782.

when first observed, varied from four weeks to twenty years, with an average of fifteen months. The basal metabolic rate ranged from +14 to +82 per cent, the average being +46 per cent. The heart rate varied in different patients from 82 to 180 a minute, with an average of 106. Arrhythmia and auricular fibrillation were present in 36 cases, or 18 per cent. Exophthalmos in varying degree was present in 134 cases, or 67 per cent.

The treatment employed by the patients prior to coming under our attention varied. Fourteen, or 7 per cent, had had thyroidectomy performed with little or no relief, 26, or 13.2 per cent, had undergone roentgen or radium therapy without marked benefit, 116, or 58 per cent, had received various forms of medical attention, particularly the administration of iodine and rest cures, and 44, or 22 per cent, had received no previous attention whatever.

It may be added that in the selection of these cases reasonable care was exercised to exclude patients presenting a dominating vagotonic symptomatology with a relatively slow heart rate. The patients selected for the use of physostigmine were dominantly of the sympatheticotonic type.

DOSAGE AND CONTRAINDICATIONS

The dosage of physostigmine employed varied between 1/60 and 1/30 grain (1 and 2 mg.) three times a day, depending on the weight of the patient. In the majority of instances the dosage of 1/30 grain three times a day was employed in patients weighing approximately 120 pounds (54.4 Kg.) or more. In those weighing less and in children, the dosage was correspondingly smaller. While it is recognized that this dosage of physostigmine salicylate is considerably in excess of the arbitrary dose, it was discovered in this series that smaller doses were scarcely capable of influencing the patient's symptomatology, and that the dosage employed was almost invariably well tolerated.

Physostigmine was administered in each case for a period of ten weeks. At the termination of this period most patients had received the maximum benefit from the drug, and it was discontinued. In those who did not show benefit from its use within three or four weeks, the drug was withdrawn.

While theoretically such symptoms as diarrhea and sweating would seem to deter the administration of physostigmine, such was rarely the case in this series. In only five cases was it necessary to discontinue the drug because of diarrhea. Indeed, in the majority of patients presenting diarrhea as a marked symptom physostigmine, by virtue of its potentiality for general improvement in circulatory and sequentially in nervous excitability, improved the intestinal function. Here we must not overlook the cases of apparent intestinal excitability resulting from

retention of or irritation by intestinal contents In such patients, diarrhea was improved because of the better elimination of intestinal residue In no instance was it necessary to withhold or withdraw physostigmine because of excessive sweating It appears that the circulatory stabilization following the administration of physostigmine is largely the corrective of cutaneous symptoms of exophthalmic goiter

COURSE OF THE DISEASE UNDER TREATMENT WITH PHYSOSTIGMINE

On the firm conviction that no single measure is capable of effecting satisfactory relief from exophthalmic goiter, these patients were also subjected to such additional measures as a high caloric diet of minimal animal protein content, a rest cure involving a stay in bed of from ten to fourteen hours (depending on the severity of the case), the administration of quinine or quinidine and an occasional medicament to overcome insomnia, digestive disturbances and other symptoms from time to time requiring attention, the correction of infectious foci wherever possible, and finally, the application of practical psychotherapy which in occasional instances extended to relatives or friends interested in the patient's welfare

With a view to checking up the benefit assignable to the administration of physostigmine alone, the records of another 100 cases of exophthalmic goiter in which no physostigmine was given were studied as controls These patients were otherwise managed in exactly the same manner as were those to whom physostigmine was administered It was found that in patients receiving the drug the results obtained, particularly those referable to the heart, occurred several weeks before tangible improvement in patients not receiving physostigmine, and the tendency toward the cyclic flaring up of symptoms or crises (either spontaneous or induced by psychic trauma) was decidedly less frequent

Primarily the object of the administration of physostigmine was the lowering of the heart rate Not alone was this accomplished in 146 cases, or 73 per cent, of this series, but in the majority, the force of the heart's action was reduced to the extent of the total elimination of subjective complaints referable to the precordium Commonly the patient would remark that the thumping of the heart against the ribs and the consciousness of the heart's action had disappeared

In patients suffering with auricular fibrillation, physostigmine alone seemed more efficacious than quinidine alone, but the combination of physostigmine and quinidine was very efficacious in the control of cardiac excitability and the restoration of rhythm The combination of physostigmine salicylate, 1/30 grain, and quinidine sulphate, 5 grains (0.324 Gm.), three times a day, was employed

Irrespective of the form of treatment adopted in exophthalmic goiter, improvement in exophthalmos is generally observed to be tardy. Even under expert thyroidectomy not only does exophthalmos persist in a large percentage of cases, but in some patients with exophthalmic goiter without exophthalmos this symptom develops postoperatively.⁸ At best, improvement in exophthalmos is among the last events in the clearing up of the syndrome, and in many patients the eyes never become normal. A measure to improve exophthalmos in a more or less specific fashion has been the crying need through the years. In view of the results observed in this series of patients, it is felt that the administration of physostigmine is the closest approach to such a measure. The results were gratifying in many instances. The eyes of patients under treatment with physostigmine are apt to improve simultaneously with manifest improvement elsewhere, and a good percentage of patients with and without a history of thyroidectomy suffering with residual exophthalmos of years' duration has been greatly benefited or completely relieved of this distressing symptom.

VARIABLES IN RESULTS OF THE ADMINISTRATION OF PHYSOSTIGMINE

The patients who were benefited to the greatest degree by the administration of physostigmine may be classified under six headings: (1) the extremes of age, i. e., patients under 14 and above 50, (2) those approaching remission after having had one or more crises, (3) sufferers from this disease over a period of four or more years, i. e., the chronic or protracted forms of exophthalmic goiter, (4) those presenting a basal metabolic rate of less than +40 per cent, (5) those presenting extreme exophthalmos, and (6) those presenting cardiac arrhythmia, especially auricular fibrillation.

On the other hand, patients who were least benefited by the administration of physostigmine were young adults presenting a basal metabolic rate of +40 per cent or higher and those who were obviously in crisis associated with rather marked cerebral excitation. However, the use of this drug was generally productive of good results when the crisis was passed.

END-RESULTS

Since statistical records of subjects with exophthalmic goiter would of necessity require the personal following up of those dubbed "cured" or "recovered" for a minimum of from three to five years, it is not in the scope of this paper to discuss the matter of end-results in this series of patients. This series has not been observed for a time of

⁸ Zimmerman, L. M. Exophthalmos Following Operations for the Relief of Hyperthyroidism, *Am J M Sc* **178** 92, 1929

sufficient length to permit of statements pertaining to end-results. In 98 patients, or 49 per cent, the pulse rate has remained normal and there is a maintenance of the general improvement to date. From present indications it appears likely that at the termination of a follow-up period of sufficient duration, the statistical records will compare favorably with those proceeding from other modes of treatment in the management of these patients. This will be the subject of another contribution in the course of time.

SUMMARY AND CONCLUSIONS

1 The results of the administration of physostigmine for a period of ten weeks in 200 cases of active exophthalmic goiter are discussed.

2 In ninety-eight, or 49 per cent, the benefit obtained was highly encouraging and may be lasting, in forty-eight, or 24 per cent, the benefit was transient though tangible, and in the remaining fifty-four, or 27 per cent, no benefit was discerned.

3 Excepting in five patients suffering from persistent diarrhea, no contraindications or untoward results were noted from the administration of physostigmine salicylate in doses corresponding to 1/30 grain three times a day in adults.

4 The most satisfactory results were noted (1) in the extremes of age, i. e., in patients under 14 and above 50, (2) in those approaching remission after having had one or more crises, (3) in sufferers from this disease over a period of four or more years, i. e., the chronic or protracted forms of exophthalmic goiter, (4) in those presenting a basal metabolic rate of less than +40 per cent, (5) in those presenting extreme exophthalmos, and (6) in those presenting cardiac arrhythmia, especially auricular fibrillation.

5 The improvement in the behavior of the heart was the first effect noted. A reduction in rate and force of the heart's action was followed by improvement in the basal metabolic rate and all subjective and objective manifestations of the disease.

6 Improvement in exophthalmos in many instances of chronic and stubborn cases was very gratifying. In a few cases of postoperative recurrence with excessive exophthalmos, physostigmine was particularly satisfactory in results.

7 From the observations herein noted it appears that physostigmine deserves high regard in the management of exophthalmic goiter.

STAINING OF RETICULOCYTES BY BRILLIANT CRESYL BLUE

INFLUENCE OF SOLUTIONS OF SUBSTANCES

CLARK W HEATH, M D

AND

GENEVA A DALAND, S B

BOSTON

In recent years it has become more and more certain that the increase in the circulation of young red blood cells, which contain reticular substance when supravitaly stained, is indicative of increased erythropoiesis. Clinical proof of this has been obtained by innumerable examples of the production of reticulocyte crises in response to various therapeutic procedures, and notably in cases of pernicious anemia following the institution of liver therapy, first described by Minot and Murphy.¹ As the importance of these young cells becomes more evident, the nature and behavior of the reticular or basophilic substance contained within them are arousing an increasing amount of interest. This basophilic substance in erythrocytes, closely related to the maturation of these cells, may well be a type of substance present in many other cells, and indeed may prove to be important in the elucidation of many clinical problems, notably those concerned with neoplastic diseases. The red blood cell, because of its clear cytoplasm, lends itself to ease of study of visible inclusions, the observation of which in other cells is hindered by their more complicated structure.

Although much remains to be learned about the basophilic substance present in reticulocytes, certain definite information has been obtained by various investigators. These data have been reviewed briefly in another paper,² in which we discussed the maturation of reticulocytes. It is a generally accepted fact that diffuse basophilia and reticular substance are identical, the latter being a manifestation of the former, pro-

¹ Submitted for publication Nov 6, 1930

² From the Thorndike Memorial Laboratory, Boston City Hospital and the Department of Medicine, Harvard Medical School

³ The expenses of this investigation were borne in part by grants from the J K Lilly gift to the Medical School of Harvard University

1 Minot, G R, and Murphy, W P. Treatment of Pernicious Anemia by a Special Diet, *J A M A* **87** 470 (Aug 14) 1926

2 Heath, C W, and Daland, G A. The Life of Reticulocytes. Experiments on Their Maturation, *Arch Int Med* **46** 533 (Sept) 1930

duced by the supravital action of certain dyes (Hawes,³ Bruckner and Spatz,⁴ Schilling-Torgau,⁵ Schilling,⁶ Key⁷ and Gawrilow⁸) The fact that the basophilic substance has different appearances for different conditions of staining has attracted much attention Bruckner⁹ pointed out that the drying of red blood cells at elevated temperatures (from 60 to 100 C) produces relatively more polychromatophilia than granulation, whereas lower temperatures produce more granulation than polychromatophilia He stated that the relative number of polychromatophilic and granular cells is a function of the temperature and the moisture of the air in which they have been dried The presence of diffuse basophilia and the absence of reticulation in ordinary Romanowsky stained preparations (Wright's stain) are explained by the action of strong fixing agents, such as methyl alcohol Sudden fixing, as with osmic acid vapor, and subsequent staining produce the appearance of diffuse basophilia Key⁷ stated that a picture resembling punctate basophilia could be obtained by heating reticulated cells to 50 C for one-half hour or by treating them with dilute potassium hydroxide Brookfield,¹⁰ by using weaker solutions of brilliant cresyl blue, found that reticulation became fragmented and resembled stippling, and that diffuse basophilia was present under such conditions Schilling⁶ described the net structure, or reticular substance, as a coarse, precipitated form of the diffusely spread material, giving the appearance termed polychromasia Hawes³ made counts of the basophilic cells and reticulocytes of the blood of various patients and found the percentage of basophilic cells always slightly lower than the percentage of reticulated cells He explained

3 Hawes, J B A Study of the Reticulated Red Blood Corpuscle by Means of Vital Staining Methods Its Relation to Polychromatophilia and Stippling Boston M & S J **161** 493, 1909

4 Bruckner, H, and Spatz, R Ueber die Beurteilung des roten Blutbildes bei der Bleivergiftung unter Berücksichtigung verschiedener Darstellungsmethoden der polychromaten und basophil punktierten Erythrocyten, Arch f Hyg **97** 277, 1926

5 Schilling-Torgau, V Arbeiten über die Erythrozyten I Ueber die polychromatophilic und verwandte Zustände, Folia haemat **11** 327, 1911

6 Schilling, V Die Zelltheorie des Erythrocyten als Grundlage der klinischen Wertung anämischer Blutbefunde, Virchows Arch f path Anat **234** 548, 1921

7 Key, J A Studies on Erythrocytes, with Special Reference to Reticulum, Polychromatophilia and Mitochondria, Arch Int Med **28** 511 (Nov) 1921

8 Gawrilow, R Zur Lehre über die vitalfarbbare Substanz der Erythrozyten, Folia haemat **38** 216, 1929

9 Bruckner, H Arbeiten über die basophile Substanz in den jugendlichen roten Blutkörperchen II Ueber die physikalisch-chemischen Eigenschaften der basophilen Substanz in den jugendlichen Erythrocyten, Arch f Hyg **98** 95, 1927

10 Brookfield, R W Blood Changes Occurring During the Course of Treatment of Malignant Disease by Lead, with Special Reference to Punctate Basophilia and the Platelets, J Path & Bact **31** 277, 1928

this by the fact that it is difficult to distinguish a cell with a small amount of basophilia from a nonbasophilic cell, while it is easy to distinguish a reticulated cell with a small amount of reticular material from a non-reticulated cell. The two counts were parallel, and Hawes considered the two types different manifestations of the same substance.

When liver therapy was first being employed in cases of pernicious anemia, the mechanism of the action of the active principle in liver on the production of red blood cells stimulated Dr. George R. Minot to investigate the effect of liver extracts on reticulocytes. It was recognized that an *in vitro* method of determining the potency of liver extracts would be of great value. Efforts to obtain such a method met with no success, but the peculiar influence of extracts of liver and other substances on the staining of reticulocytes seemed to warrant special study.¹¹

METHODS

Since Cesaris-Demel¹² published accounts of the supravital action of brilliant cresyl blue on reticulocytes, this dye has been widely used in the study of these cells. A solution of 0.5 per cent brilliant cresyl blue (National Aniline Company) in 95 per cent ethyl alcohol was used in the experiments to be described.

Blood was obtained from patients and from rabbits. Reticulocytosis was produced in the rabbits by the intraperitoneal injection of phenylhydrazine or by bleeding. The blood of patients with pernicious anemia at the height of the reticulocyte rise, following liver therapy, served as the source for human reticulocytes. The blood was collected under sterile precautions, placed in a sterile flask containing glass beads and defibrinated by gentle shaking. Sometimes, if the number of reticulocytes was low, the blood was centrifugated to concentrate the young cells at the top of the column of blood.

The substances to be tested were dissolved in distilled water, in physiologic solution of sodium chloride or in a buffer solution, composed of 0.12 molar of disodium phosphate and 0.03 molar of monosodium phosphate. Certain solutions of amino-acids and liver extracts were neutralized with sodium hydroxide, bromthymol blue being used as an indicator. As a rule, 0.4 cc of solution was mixed with 0.2 cc of blood in a small test tube. After the cells and solution had been in contact for a certain period of time, the test tube was shaken thoroughly and a small drop smeared between two cover slips on which brilliant cresyl blue had previously been dried. The cresyl blue smears were dried in the air and counter-stained with Wright's stain (a modification of the Romanowsky stain, in which fixation is produced by methyl alcohol) after the methods of Hawes³ and Cunningham.¹³ Control preparations of the original blood were made in a similar manner. Permanent preparations mounted in balsam were studied for the relative numbers of cells showing diffuse basophilia and those showing reticular substance.

11 Drs. George R. Minot, Franklin R. Miller, Samuel S. Ellis and J. Seabury Hathaway of this laboratory did the pioneer work on this subject.

12 Cesaris-Demel, A. Studien über die roten Blutkörperchen mit den Methoden der Färbung in frischen Zustände, *Folia haemat.* 4 1, 1907.

13 Cunningham, T. D. A Method for Permanent Staining of Reticulated Red Cells, *Arch. Int. Med.* 26 405 (Oct.) 1920.

One thousand cells were counted, and the percentage of reticulocytes determined. In some cases the percentage of basophilic cells was also determined.

Some experiments were performed with cells washed free from serum with physiologic solution of sodium chloride. No marked difference was observed between the staining character of cells left in their own serum and cells washed free from serum, but the latter tended to hemolyze more easily than the former. A more pronounced effect of a substance could sometimes be demonstrated by the use of 0.6 cc or 0.8 cc of solution and 0.2 cc of blood.

In the first series of experiments, 10 per cent solutions of the substances were usually used to test their effect on the staining of reticulocytes by brilliant cresyl blue. If this concentration was too toxic to red cells, as shown by hemolysis of the cells in preliminary test tube experiments or by the disintegration of the cells in the process of fixing and staining, such weaker strengths of the solutions were employed as did not produce these changes in the red blood cells.

THE INFLUENCE OF SOLUTIONS OF DIFFERENT SUBSTANCES

A summary of the results of experiments in which a variety of organic and inorganic substances was used is recorded in table 1. After the blood had remained in contact with a solution for about fifteen minutes and the smears had been stained, the percentage of reticulocytes, in most instances, diminished markedly, or the reticulocytes apparently entirely disappeared. A study of the preparations, however, revealed the presence of many diffusely basophilic cells, the number of which varied with the number of reticulocytes seen in the control preparations. Examples of such observations are shown in table 2. When only a few reticulocytes remained, diffusely basophilic cells were also seen. Cells which were diffusely basophilic in such preparations frequently contained strands of reticular substance or fine granules of basophilic staining substance. Cells could be found which varied greatly in the relative amounts of diffuse basophilia and reticular substance which they contained.

A wide variety of substances was chosen in order to determine whether or not this effect, antagonistic to the staining of reticular substance, was related to any one class of substances. It is evident from the data in table 1 that there was no such relationship. Organic and inorganic substances, strong and weak electrolytes and acids and bases produced this effect.

The substances most thoroughly studied were liver extracts¹⁴. Two typical examples of their effect on the staining of reticular substance are shown in table 1. Studies were made on liver extracts which were potent but which were impotent when given to patients with pernicious anemia. The influence of these extracts on the staining of reticulocytes bore no relation to their potency.

¹⁴ Many of these were prepared by Dr. Edwin J. Cohn and his associates (Cohn, E. J., Minot, G. R., Alles, G. A., and Salter, W. T. *The Nature of the Material in Liver Effective in Pernicious Anemia*, *J. Biol. Chem.* **77**: 325, 1928).

TABLE 1—*The Influence of Solutions of Substances on the Staining of Reticulocytes with Brilliant Cresyl Blue*

Substance	Concen- tration of Solution, per Cent	Amount of Solution, Cc	Amount of Defibrinated Blood, Cc	Reticulocytes	
				Control, per Cent	After 15 Min Exposure to Solution, per Cent
Liver extract no 343 (N N R)	15.0	0.4	0.2	29.3	5.8
Purified extract RI XLII*	10.0	0.4	0.2	12.2	0.6
Glycine	10.0	0.4	0.2	36.7	3.0
Alanine	10.0	0.4	0.2	36.7	10.2
Leucine	10.0	0.4	0.2	36.7	0.6
Glutamine acid	1.0 (saturated)	0.4	0.2	20.0	10.6
Cystine	Saturated	0.4	0.2	27.1	24.4
Aspartic acid	Saturated	0.4	0.2	27.1	1.0
Sodium asparaginate	10.0	0.4	0.2	27.1	4.1
Creatinine	8.7	0.4	0.2	36.7	3.6
Dextrose	8.0	0.8	0.2	34.3	2.2
Glycolic acid	±0.3	0.4	0.2	36.7	32.0
Phenylhydrazine	2.0	0.4	0.2	36.7	33.6
Leucithin	Small particles (insoluble)		0.2	27.1	29.0
Cholesterol	Small crystal (insoluble)		0.2	27.1	±30.0†
Peptone	10.0	0.4	0.2	26.6	17.2
Sodium chloride	2.5	0.6	0.2	29.4	0.4‡
Sodium chloride	2.5	0.4	0.2	21.2	3.4
Sodium iodide	2.5	0.4	0.2	19.8	0.0
Sodium sulphate	10.0	0.4	0.2	30.1	4.0
Sodium acid phosphate	5.0	0.8	0.2	19.8	11.2
Calcium chloride	7.5	0.4	0.2	26.6	0.0
Magnesium sulphate	10.0	0.4	0.2	30.1	0.0
Sodium hydroxide	0.001N	0.4	0.2	15.8	9.3
Hydrochloric acid	0.05N	0.4	0.2	15.8	10.6
Ammonium hydroxide	1.0	0.4	0.2	26.6	19.4
Acetic acid	0.1	0.4	0.2	26.6	5.2
Lactic acid	0.1	0.4	0.2	15.8	16.4
Ammonium acetate	10.0	0.4	0.2	26.6	19.4
Hydrogen peroxide	5.0	0.4	0.2	26.6	26.6
Glutathione	5.0	0.1	0.4	18.8	0.0
Pituitary extract (Lederle)		0.4	0.2	12.2	0.0
Epinephrine chloride 1:1,000		0.4	0.2	15.8	1.6
Thyroxin	Crystals		0.2	12.2	12.0

* Prepared by Dr. Edwin J. Cohn

† Considerable injury to the red blood cells prevented accurate counting

‡ Five minute exposure

TABLE 2—*Presence of Basophilic Cells and Reticulocytes After Contact with Different Solutions*

Substance	Concentration of Solution	After 15 Min. Contact With Solution Relative Number of Cells Showing	
		Reticular Material, per Cent	Diffuse Basophilia, per Cent
Control	Defibrinated blood	21.4	0
Control	Buffer solution and defibrinated blood	17.6	0
Liver extract no 343 (N N R)	20%	9.6	3.4
	20%	11.1	4.8
Glycine	10%	1.6	6.0
	10%	1.8	6.0

As these liver extracts were known to be rich in amino-acids, the latter alone were next studied. Glycine, alanine and leucine inhibited the staining of reticular substance by brilliant cresyl blue in a manner similar to that of corresponding strengths of liver extract no 343 (N N R). Cystine, in a dilute solution, had only a slight inhibiting effect. It is noteworthy that the two dibasic amino-acids, glutaminic and aspartic acids, had as strong an inhibiting influence as the monobasic acids, although their slight solubility allowed the use of only weak solutions. Dextrose behaved similarly to liver extracts and the amino-acids. In some qualitative experiments sucrose also had an inhibiting influence.

Sodium salts, calcium chloride and magnesium sulphate inhibited the staining of reticulocytes, the last two being apparently more effective than the sodium salts. The presence of a bivalent cation may account for this difference. Sodium hydroxide, hydrochloric acid, ammonium hydroxide and acetic acid, although they could be employed only in very small concentrations, seemed to have some inhibiting influence. Lactic acid, in one experiment, had no influence. Hydrogen peroxide itself was not effective. When added to a solution of liver extract or glycine, hydrogen peroxide did not alter the inhibiting effect of these substances on the staining of reticulocytes.

Extracts of pituitary and epinephrine were tested to compare their action with that of liver extracts, and they were found to have a similar inhibiting influence. Insulin, the action of which on the permeability of erythrocytes has been the subject of many reports,¹⁵ likewise seemed to be effective. However, as insulin was toxic to the red blood cells in the strength employed, it became impossible to count the reticulocytes accurately.

The presence of diffuse basophilia in these preparations was as much a criterion in the estimation of the influence of a substance on the staining of reticulocytes as the actual reduction in the number of cells showing reticular material. When the influence of substances insoluble in water, such as cholesterol, lecithin and thyroxin, was studied, no diffuse basophilia could be seen, and there was no reduction in the number of reticulocytes. Therefore, these substances when added to blood were noneffective.

There is necessarily a limitation of the number of substances that can be tested in this manner, because of injury to the red blood cells which is caused when strong concentrations are used, whereas weak concentrations will not affect the cresyl blue staining. Such, for example, are urea, malonic acid, trivalent salts such as ferric chloride and

15 Haldane, J. B. S., Kay, H. D., and Smith, W. The Effect of Insulin on Blood Volume, *J. Physiol.* **59** 193, 1924. Irving, J. T., and Kay, H. D. The *In Vivo* Permeability of the Red Corpuscles of the Rabbit, *J. Physiol.* **61** 113, 1926.

sodium phosphate, potassium chloride, sodium bromide, strontium chloride and magnesium chloride

In summary, it may be stated that all easily soluble substances so far experimented with, which are not toxic enough to red blood cells to produce hemolysis or severe injury, have an inhibiting influence on the staining of reticulocytes by brilliant cresyl blue

It may be argued that such strong concentrations of substances produce permanent changes of the membranes of the red blood cells or even "fixing" of the red blood cells, thus preventing the entrance of brilliant cresyl blue into the cells. That this is not likely is shown by the following experiment: red blood cells were left in contact with a solution of liver extract or glycine, then the cells were washed several times by centrifugation and the addition of physiologic solution of sodium chloride or buffer solution, if the cells were then stained supravitaly the reticulocytes appeared as originally, and diffuse basophilia was absent. Therefore, the liver extract or glycine inhibited the staining of the reticular material only as long as the test substance remained in contact with the red blood cells.

Reticulated cells stained as usual if they were crenated by exposure to a small amount of alcohol, showing that crenation is not a factor in the inhibitive influence of these substances.

Preparations were examined in the moist state after supravital staining with brilliant cresyl blue, but without fixing and counterstaining with Wright's stain. The influence of solutions of substances was seen to be the same here as in the fixed preparations, no or few reticulocytes were observed. Under these circumstances, on gross as well as microscopic inspection of the smears, there seemed to be an inability of the dye to "take," and the red blood cells tended to remain unstained.

No definite difference between the effects on rabbit and human reticulocytes was found in these experiments. The human blood was more satisfactory because the cells withstood injury better and more perfect preparations could be made.

THE INFLUENCE OF DIFFERENT CONCENTRATIONS OF SUBSTANCES

Table 3 shows the results when different concentrations of liver extract, calcium chloride and sodium chloride were used. The inhibiting influence of these substances on the staining of reticulocytes by brilliant cresyl blue varies with the strength of the solution of the substance. This was less true of sodium chloride in concentrations higher than 2.5 per cent when the cells tended to hemolyze in the process of smearing, which rendered counting difficult. That very dilute solutions can have an influence is seen from the data in table 3 in the cases in which 0.5 per cent calcium chloride and 0.5 per cent sodium chloride were

used. It was noticed that physiologic solution of sodium chloride, or phosphate buffers, particularly if potassium were present, had a slight inhibiting influence (table 2). This was more apparent in the actual microscopic study of the preparations, in which poorly defined reticular substance or cells with diffuse basophilia and a few fine threads of reticular substance were present. These cells were counted as reticulocytes in the quantitative experiments. Preparations in which only diffusely basophilic cells and no reticulocytes were present were usually those in which very strong concentrations of substances were used.

TABLE 3—*The Influence of Different Concentrations of Substances on the Staining of Reticulocytes (0.4 cc of Solution Added to 0.2 cc of Defibrinated Blood)*

Substance	Concentration of Solution, per Cent	Period of Exposure, Minutes	Reticulocytes	
			Control, per Cent	After Exposure to Solution, per Cent
Liver extract no. 343 (N. N. R.)	20.0	20	13.0	1.5
	10.0	20	13.0	4.6
	5.0	20	13.0	11.9
	1.0	20	13.0	12.8
Calcium chloride	10.0	15	21.2	0.4
	5.0	15	21.2	1.8
	2.5	15	21.2	11.8
	0.5	15	21.2	17.8
Sodium chloride	10.0	15	21.2	0.8
	5.0	15	21.2	9.8
	2.5	15	21.2	3.4
	0.5	15	21.2	20.2
Sodium chloride*	6.0	1	16.6	3.3
	1.0	1	16.6	4.9
	3.5	1	16.6	7.3
	3.0	1	16.6	6.8
	2.5	1	16.6	8.8
	2.0	1	16.6	10.8

* In this experiment 0.1 cc of 0.4 per cent brilliant cresyl blue was added to the mixture and smears were taken one minute later, plain cover slips being used.

INFLUENCE OF SOLUTIONS OF SUBSTANCES IN CONTACT WITH RETICULOCYTES FOR VARYING PERIODS OF TIME

When an effective solution was left in contact with the cells for an hour or more, the percentage of reticulocytes tended to return to the original value, that is, the substance tended to lose its inhibiting influence on the staining of the reticular substance by the dye (table 4). This has not always been true, as in the case of dextrose. Certain preparations and certain strengths of solutions have failed to show this effect. However, the effect has repeatedly been demonstrated for liver extracts. The effect was more pronounced when the experiments were carried out at 37.5 C than at room temperature. That this phenomenon, namely, the weakening of the inhibiting influence of substances when left in contact with cells for an hour or more, could not

be due to the gradual breaking down of amino-acids or polypeptids¹⁶ is shown by the fact that sodium chloride acts in a manner similar to liver extract and amino-acids

If the mixtures are left in the incubator for longer than several hours, the percentage of reticulocytes begins to diminish, a process which has been described elsewhere² and which is believed to be one of maturation of the reticulocytes

COMMENT

It is assumed from these studies that the presence of diffuse basophilia in a cell indicates that the brilliant cresyl blue has not acted on the basophilic substance to change it to reticular substance. This may be due either to the inability of the dye to enter the cell or to the inability of the dye already in the cell to produce its characteristic precipitation-like action on the basophilic substance. That it is related to the permeability of the red blood cell to brilliant cresyl blue seems more probable. Both conditions are representative of extremely complicated mechanisms, and it is impossible at the present time to do more than conjecture as to the exact nature of the phenomenon. Gawrilow³ discussed thoroughly problems concerning the "vital" staining substance in young red blood cells and stated that a more thorough physical and colloidal chemical knowledge of this substance is needed for its better understanding.

It is unlikely that the dye is altered chemically or that it is oxidized to a colorless compound, because the inhibiting effect on the staining of reticulocytes is produced by so many different kinds of substances. Alteration in p_H has little to do with the phenomenon as a whole, although it may well modify the results to some extent. Variations in staining cells under extracellular conditions of different p_H were noted by Irwin,¹⁷ Brooks,¹⁸ Ochs,¹⁹ Tolstouhov²⁰ and Gawrilow³

16 Hiruma, K. On the Fate of Amino-Acids Permeated into the Red Corpuscles, Japan M. World **2** 65, 1922

17 Irwin, M. The Penetration of Basic Dye into Nitella and Valonia in the Presence of Certain Acids, Buffer Mixtures, and Salts, J. Gen. Physiol. **10** 271, 1926, Certain Effects of Salts on Penetration of Brilliant Cresyl Blue into Nitella, *ibid.* **10** 425, 1927, The Effect of Acetate Buffer Mixtures, Acetic Acid, and Sodium Acetate on the Protoplasm, as Influencing the Rate of the Penetration of Cresyl Blue into the Vacuole of Nitella, *ibid.* **11** 111, 1927, Counteraction of the Inhibiting Effects of Various Substances on Nitella, *ibid.* **11** 123, 1927

18 Brooks, M. M. Studies on Permeability of Living Cells. IX. Does Methylene Blue Itself Penetrate? Univ. California Publ. Zool. **31** 79, 1927

19 Ochs, G. W. Ueber den Einfluss der Temperatur auf die Färbung von Blutausschlag-Präparaten, Folia haemat. **37** 241, 1928

20 Tolstouhov, A. V. Effect of Preliminary Treatment on Staining Properties of the Tissues, Stain Technology **3** 49, 1928

Gawrilow considered of importance the hydrogen ion concentration of the aqueous medium in which the supravital staining of reticulocytes takes place. He placed red blood cells of guinea-pigs in Sorenson's phosphate buffer mixtures and stained them supravitaly with polychrome methylene blue (methylthionine chloride, U S P), counterstaining them with giemsa. In alkaline mediums an outstanding network was seen, in acid mediums very little network was observed, but much basophilia, in intermediate solutions all degrees of basophilia and network appeared. This influence of the p_H undoubtedly varies for the dye used and for the experimental conditions under which the staining takes place, for we have found that brilliant cresyl blue with a similar range of p_H stains the reticulocytes uniformly by our experimental methods. Also, phosphate buffer itself may have a certain inhibiting effect on the staining of reticulocytes.

Instances of the inhibiting influence of substances on the permeability of cell membranes are numerous in the literature. Hober and Memmesheimer²¹ found that cane sugar and glycine had a prohibitive influence on the entrance of rhodamine B, methylene blue or methyl violet B into ox blood cells. In 1894, Bremer²² and in 1897, Le Goff²³ reported poor staining of red blood cells by methylene blue in cases of diabetes, and they suggested this as a test for diabetes. The phenomenon apparently depends on the presence of increased amounts of dextrose in the blood. Loeb²⁴ described what he named the "antagonistic salt action." Solutions of electrolytes, such as sodium chloride and calcium chloride in certain concentration, inhibited the entrance of potassium chloride or acids into the embryo of eggs of *Fundulus*.

Brooks²⁵ studied the inhibiting effects of water and salts on the entrance of the dye, dahlia, into the sap of the cells of *Nitella*. She employed the following substances in the order of their power of inhibiting the entrance of the dye: distilled water, tap water, sodium chloride, potassium chloride, calcium chloride and magnesium chloride.

21 Hober, R, and Memmesheimer, A. Einige Beobachtungen über Permeabilitätsänderungen bei roten Blutkörperchen in Lösungen von Nichtletern, Arch f d ges Physiol **198** 564 1923

22 Bremer, L. Ueber eine Farbmethode, mit der man Diabetes und Glycosurie aus dem Blute diagnostizieren kann, Centralbl f d med Wissensch **32** 850, 1894

23 Le Goff, Jean-Marie. Sur certaines reactions chromatiques du sang dans le diabete sucre, These, Paris, 1897

24 Loeb, J. The Mechanism of the Diffusion of Electrolytes through the Membranes of Living Cells, J Biol Chem **27** 339, 353 and 363, 1916, **28**.175, 1916

25 Brooks, M. M. Studies on the Permeability of Living Cells. VIII. The Effect of Chlorides upon the Penetration of Dahlia into Nitella, Protoplasma **2** 420, 1927

Irwin¹⁷ found that sodium and potassium ions, phosphoric acid, hydrochloric acid, phosphate and acetate buffers and acetic acid inhibited the rate of penetration of brilliant cresyl blue into *Nitella*. A direct analogy between Brooks' and Irwin's experiments and those regarding the permeability of the membranes of the red blood cells should not be drawn, however, because in the latter case, at least, there is doubt whether we are dealing with vital phenomena (Nittis²⁶). Pearse²⁷ found that the reticulum of immature red blood corpuscles in solutions of the same p_H but of different composition reacted to neutral red in the same way as the stained structures of dead leukocytes, and the opposite to the structures within living white corpuscles. He gave this as evidence in favor of the view set forth by Key that the reticulum is an inactive substance, but he stated that since erythrocytes are not considered cytologically as true cells the semipermeable properties of their membrane may not be comparable to those of other living cells.

Kerr²⁸ noted that red blood cells become progressively more permeable to cations as the proportion of serum present decreases. He remarked that 0.85 per cent sodium chloride was not "physiologic" since it permits the transfer of ions. This opens an important lead on the problems presented here. Physiologic solution of sodium chloride inhibits the staining of reticulocytes by brilliant cresyl blue. Other substances that were employed in strong concentrations were certainly not "physiologic." That changes take place under these conditions, undoubtedly in the transfer of ions, is probable, as is shown in the experiments given in table 4, in which the inhibiting influence of the solutions is shown to diminish with time. Neuhausen and Breslin²⁹ and Mond and Gertz³⁰ studied problems related to the permeability of the membranes of red blood cells which bear especial relation to the phenomena presented in this paper.

26 Nittis, S. "Supra-Vital" Staining Phenomena of Erythrocytes, *Folia haemat* **41** 385, 1930.

27 Pearse, H. E. The Permeability of Human Blood Cells to Carbon Dioxid and Ammonium Hydroxid in Solutions of the Same p_H , *Arch Int Med* **35** 347 (March) 1925.

28 Kerr, S. E. Studies on the Inorganic Composition of Blood. III. The Influence of Serum on the Permeability of Erythrocytes to Potassium and Sodium, *J Biol Chem* **85** 47, 1929.

29 Neuhausen, B. S., and Breslin, J. E. Study of the Influence of Chemicals on Erythrocyte Membranes by Changes in Corpuscular Volume, *Bull Johns Hopkins Hosp* **34** 199, 1923.

30 Mond, R., and Gertz, H. Vergleichende Untersuchungen über Membranstruktur und Permeabilität der roten Blutkörperchen verschiedener Säugetiere, *Arch f d ges Physiol* **221** 623, 1929.

It seems unlikely that red blood cells are the only cells that contain a substance which is closely connected in some way with the maturation of cells, and which is demonstrable by certain staining methods. Unpublished data at hand indicate that a substance similarly demonstrable is present also in the white blood cells and bears a relation to the maturation changes of these cells. Therefore, it seems reasonable to conclude that studies of the sort presented in this paper tend to emphasize general, rather than special, phenomena of cell life. As knowledge

TABLE 4—*The Influence of Solutions of Substances in Contact with Blood for Some Hours on the Staining of Reticulocytes (0.4 cc of Solution Added to 0.2 cc of Defibrinated Blood)*

Substance	Period of Exposure	Percentage of Reticulocytes	
		Control Blood	After Exposure to Solution
10 per cent liver extract no. 343 (N.N.R.)	15 minutes	34.2	10.5
	50 minutes		25.7
	3 hours, 15 minutes		31.0
10 per cent liver extract no. 343 (N.N.R.)	15 minutes	34.2	23.7
	3 hours, 15 minutes		25.0
10 per cent liver extract no. 343 (N.N.R.)	15 minutes	34.2	19.1
	3 hours, 15 minutes		23.4
2.5 per cent sodium chloride	5 minutes	29.4	0.4
	2 hours		25.8
8 per cent dextrose	5 minutes	34.2	2.2
	1 hour		1.6
	2 hours		1.0
	3 hours		0.9
8 per cent dextrose*	5 minutes	29.8	0.8
	1 hour		2.1
	2 hours		1.5
2.5 per cent sodium chloride*	5 minutes	33.8	21.0
	15 minutes		17.1
	1 hour		21.4
	3 hours		18.9
2.5 per cent sodium chloride†	15 minutes	24.2	11.0
	1 hour		12.6
	3 hours		15.7
	6 hours	22.0	12.6

* These experiments were carried out at room temperature, all of the other experiments were carried out at 37.5 C.

† In this experiment 0.1 cc. of 0.4 per cent brilliant cresyl blue was added to the mixture of cells and solution, and smears on glass cover slips were taken after one minute.

concerning cellular biology accumulates it will unfold the secrets of vital processes and lead eventually to the defeat of disorders associated with the abnormal growth of cells.

CONCLUSIONS

1 A variety of substances in solution, including liver extracts, amino-acids and certain salts, have an inhibiting influence on the staining of reticulocytes by brilliant cresyl blue.

2 The influence of the liver extracts on the staining of reticulocytes is not related to the potency of the extracts for producing remission in pernicious anemia.

3 The inhibiting effect of a substance on the staining of reticulocytes varies with the concentration of the solution of the substance

4 When solutions of liver extract, amino-acids or sodium chloride remain in contact with the cells for a long time, the inhibiting influence on the staining reaction tends to diminish

5 The experiments give further evidence in support of the theory that basophilic substance and reticular substance are different manifestations of the same material

6 The inhibiting influence on the staining of reticulocytes is assumed to be due to alteration in the permeability of the red blood cells produced by the action of various substances in solution

PARAVERTEBRAL INJECTIONS OF ALCOHOL FOR THE RELIEF OF CARDIAC PAIN

A REVIEW OF EXPERIENCE TO DATE AND A REPORT OF NINE CASES *

ROBERT L. LEVY, M.D.
AND
RICHMOND L. MOORE, M.D.
NEW YORK

As experience accumulates following the introduction of a new therapeutic procedure, there comes a time when it is profitable to halt activity and critically appraise the value of what has been accomplished. Following such an analysis, ineffective measures are discarded, modifications often suggest themselves, and plans for further development of the method may be formulated. Cervical sympathectomy as a means of alleviating pain of cardiac origin has not stood the test of trial, and in America it has fallen into disuse. The many types of operation employed and the variability of results afford abundant evidence that ablation of any portions of the sympathetic chain in the neck cannot interrupt all of the nervous pathways concerned. Furthermore, the most intense suffering is encountered in patients with coronary disease, and as a rule it is inadvisable to submit such persons to an extensive surgical operation. When discomfort is so great that life becomes burdensome, any measure offering a reasonable hope of relief deserves serious consideration and trial under suitably controlled conditions. It has seemed to us timely to survey the results to date of paravertebral injections of alcohol and to record personal observations in nine cases.

REVIEW OF THE LITERATURE

The idea of paravertebral alcohol block for the relief of cardiac pain was the outcome of a logical sequence of events. Paravertebral injections of procaine hydrochloride have been used for a number of years in order to induce local anesthesia for the performance of surgical operations. In Germany, the method has been employed more recently for the differential diagnosis of various abdominal conditions by abolishing pain in segmental areas and thereby deducing its source of origin. At

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* From the Departments of Medicine and Surgery, College of Physicians and Surgeons of Columbia University and the Presbyterian Hospital.

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the suggestion of von Bergmann, Laewen¹ first practiced the injection of procaine hydrochloride into the dorsal ramus in a case of angina pectoris, but gave no detailed account of the patient or of the effects. Brunn and Mandl,² stimulated by Pal, then undertook to study the method systematically from a therapeutic point of view. Luger,³ Pal,⁴ Mandl,⁵ Brunn⁶ and others followed with reports of series of cases. After tabulating and analyzing this literature, it became apparent that the injections were made into various nerves at different cervical and thoracic levels, the clinical histories were recorded only briefly, and the relief afforded, though definite as a rule, was of relatively short duration. However, Mandl stated that in three instances the attacks disappeared for from six months to a year.

Swetlow⁷ suggested the injection of alcohol following that of procaine hydrochloride, with a view of inducing Wallerian degeneration in the fibers of the ramus communicans and thereby insuring greater permanence of relief. He undertook to map out areas of disturbed cutaneous sensibility in his patients, making injections into the roots corresponding to the segmental distribution of sensory changes. In a series of papers, Swetlow reported twenty-two cases.⁷ Nineteen cases from the Massachusetts General Hospital have been recorded at various times by White and White,⁸ Sprague and Mixter,⁹ Richardson and White,¹⁰

1 Laewen, A. Paravertebrale Novokaininjektionen zur differential Diagnose intraabdomineller Erkrankungen, *Zentralbl f Chir* **49** 1510, 1922

2 Brunn, F, and Mandl, F. Die paravertebrale Injektion zur Bekämpfung visceraler Schmerzen, *Wien klin Wchnschr* **37** 511 (May 22) 1924

3 Luger, A. Therapeutischer Versuch bei Aortalgie, *Wien med Wchnschr* **74** 2543 (Nov 22) 1924

4 Pal, J. Zur Aussprache uber Klinik der Angina pectoris, *Wien klin Wchnschr* **37** 351 (April 3) 1924

5 Mandl, F. Weitere Erfahrungen mit der paravertebralen Injektion bei der Angina pectoris, *Wien klin Wchnschr* **38** 759 (July 2) 1925

6 Brunn, F. Zur Behandlung der Angina pectoris mit paravertebralen Injektion, *Wien klin Wchnschr* **39** 110 (Sept 23) 1926

7 Swetlow, G I. Paravertebral Alcohol Block in Cardiac Pain, *Am Heart J* **1** 393 (April) 1926. Swetlow, G I, and Schwartz, S P. The Treatment of Cardiac Pain by Paravertebral Alcohol Block, *J A M A* **86** 1679 (May 29) 1926. Swetlow, G I. A Clinicophysiology Study of the Pathway of Pain Impulses in Cardiac Disease, *Am J M Sc* **178** 345 (Sept) 1929, Angina Pectoris. Paravertebral Alcohol Block for the Relief of Pain, *Am J Surg* **9** 88 (July) 1930

8 White, J C, and White, P D. Angina Pectoris. Treatment with Paravertebral Alcohol Injections, *J A M A* **90** 1099 (April 7) 1928

9 Sprague, H B, and Mixter, W J. A New Method for the Treatment of Severe Angina Pectoris, *New England J Med* **200** 199 (Jan 24) 1929

10 Richardson, E P, and White, P D. Sympathectomy in the Treatment of Angina Pectoris. Comparison of Results with Those from Paravertebral Alcohol Injection, *Am J M Sc* **177** 161 (Feb) 1929

Mixter and White¹¹ and White¹² Pletnew and Hesine¹³ reported the administration of seventy-three injections in eighteen patients, and Cattell and Hurxthal¹⁴ published the account of another case from the Lahey Clinic in Boston. Including the nine cases in our own series, there are available records of sixty-eight patients who received injections of alcohol.

ANATOMY AND PHYSIOLOGY OF THE NERVES CONCERNED IN THE MECHANISM OF CARDIAC PAIN

Knowledge concerning the nervous pathways by which painful impulses are transmitted from the heart and aorta to the central nervous system is still incomplete. Certain facts have been established with reasonable certainty, and in this brief summary the attempt will be made to remain within the domain of probability rather than to wander in the realm of the possible. The following statements, as well as the accompanying diagram (fig 1), are based largely on the work of Langley,¹⁵ Edgeworth¹⁶ and Ranson¹⁷.

In the words of Ranson

Whether or not the intense pain which characterizes the anginal attacks is due to stretching of a diseased aorta, to spasm of the coronary arteries, or to anemia of the myocardium, the pain in itself clearly indicates that there is an irritation of sensory fibers in the heart wall or in the immediately associated arteries.

These sensory fibers form a plexus surrounding the coronary vessels and aorta, and in this plexus minute sympathetic ganglions are found. The course of the sensory fibers for the heart and its associated arteries is fairly well known (fig 1). Afferent impulses are carried to the

11 Mixter, W. J., and White, J. C. Alcohol Injection in Angina Pectoris, *Ann Surg* **89** 199 (Feb.) 1929.

12 White, J. C. Angina Pectoris. Relief of Pain by Paravertebral Alcohol Block of the Upper Dorsal Sympathetic Ramus, *Arch Neurol & Psychiat* **22** 304 (Aug.) 1929, Angina Pectoris. Treatment by Paravertebral Alcohol Injection or Operation Based on the Newer Concepts of Cardiac Innervation, *Am J Surg* **9** 98 (July) 1930.

13 Pletnew, D. D., and Hesine, V. R. Paravertebral Injections for Angina Pectoris, *Klin med* **6** 797, 1928. (The original of this paper was not available. A translated abstract was obtained from the Surgeon-General's Library, Washington, D. C.) Pletnew, D. D. Die Anwendung systematischer paravertebraler Injektionen bei der Behandlung der Angina Pectoris, *Med Welt* **4** 848 (June 14) and 884 (June 21) 1930.

14 Cattell, R. B., and Hurxthal, L. M. Paravertebral Alcohol Injection for Angina Pectoris, *J A M A* **92** 1519 (May 4) 1929.

15 Langley, J. N. The Sensory Nerve Fibers of the Heart and Aorta in Relation to Surgical Operations for the Relief of Angina Pectoris, *Lancet* **2** 955 (Nov. 8) 1924.

16 Edgeworth, F. H. On a Large-Fibred Sensory Supply of the Thoracic and Abdominal Viscera, *J Physiol* **13** 260, 1892.

17 Ranson, S. W. The Cardiac Nerves in Angina Pectoris, *Am Heart J* **1** 508 (April) 1926.

spinal cord along the cardiac branches of the middle and inferior cervical sympathetic ganglions (middle and inferior cardiac nerves) and pass through the sympathetic trunk and into the upper five (possibly six) thoracic nerves through the corresponding white rami communicantes. Thus, in accordance with Head's¹⁸ demonstration that the pain of visceral disease is referred to the cutaneous segmental areas in the distribution of the nerves supplying a viscus, pain of cardiac origin is referred chiefly to the wall of the chest and the inner aspect of the left arm,

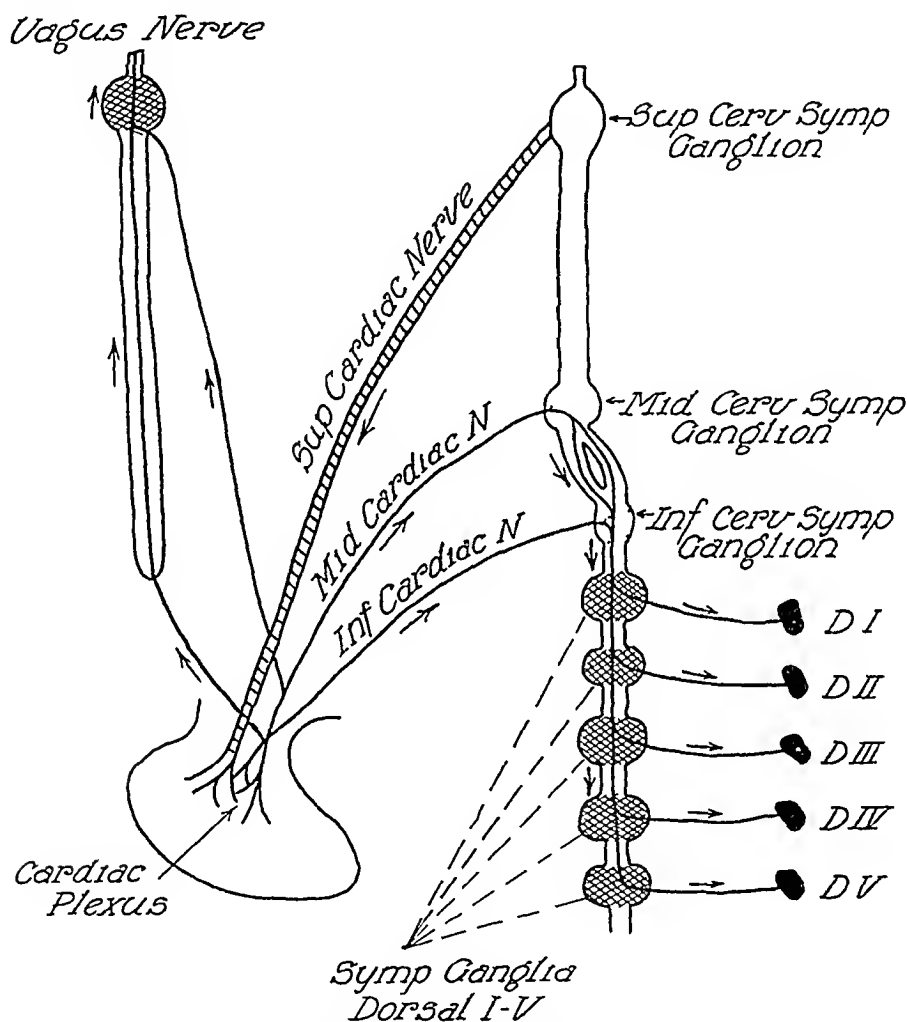


Fig 1—Diagram showing the nervous pathways concerned in the origin and transmission of cardiac pain. Note that the superior cardiac nerve conducts only motor impulses.

corresponding to the distribution of the first five dorsal nerves. Afferent impulses from the heart are also carried to the brain along the vagus and may cause pain referred to the head through communicating branches to the third, fourth and fifth cranial nerves.

No afferent fibers from the heart to the superior cervical sympathetic ganglion have been demonstrated, and for the present the superior

¹⁸ Head, H. On Disturbances of Sensation, with Especial Reference to the Pain of Visceral Disease, *Brain* **16** 99, 1893, **19** 153, 1896.

cardiac nerve must be regarded as entirely motor. In certain cases, particularly those of Coffey and Brown,¹⁹ relief from painful paroxysms has been obtained following the removal of only the superior cervical sympathetic ganglion. To explain this observation, Holmes and Ranson²⁰ have advanced the hypothesis that vasoconstrictor fibers reach the cardiac plexus from this ganglion by way of the superior cardiac nerve. Under these conditions, the painful seizures are due to coronary spasm. This mechanism might well explain the paroxysms in patients showing at necropsy no morbid changes in the heart or in its vascular bed, as exemplified by the case reported by one of us (Levy²¹).

In view of the number of afferent pathways from the heart to the cord and the brain and with the possibility of individual variation from a standard pattern being taken into account, the difficulty of interrupting all of these paths by cervical sympathectomy becomes apparent. On theoretical grounds, paravertebral injections of alcohol should afford a better chance for success with less trauma, as they interrupt the passage of painful impulses at their point of entrance to the spinal cord. However, impulses can still be transmitted to the cranial nerves through the vagus, and vasoconstriction of the coronaries may still be possible via the superior cardiac nerve. Probably other uncharted pathways are concerned.

TECHNIC OF PARAVERTEBRAL INJECTIONS

The technic employed by previous workers as well as by us is the one described by Labat²². It has been given in detail by Swetlow,²³ and certain slight modifications have been suggested by White and White⁸. No attempt was made in our patients to determine into which roots injections should be made by mapping out areas of disturbed sensibility of the skin. It was frequently impossible to delimit definite levels, and it was believed that by making injections into the first five dorsal rami, the main known sensory pathways to the cord were interrupted.

In all of our cases injections were made in the same way. The patient was placed on the right side, with knees bent and drawn toward the chin. The skin was prepared with iodine, and the spines of the first five dorsal vertebrae were marked with acriflavine. Dots were made 4 cm. to the left of each dorsal spine, and the skin was infiltrated with a 1 per cent solution of procaine hydrochloride at each of these points. A needle 8 or 10 cm. in length was inserted through each wheal, perpendicularly to the skin, until it touched the border of the underlying rib. The direction of the needle was then shifted so that it pointed mesially

19 Coffey, W. B., and Brown, P. K. The Surgical Treatment of Angina Pectoris, *Arch Int Med* **31** 200 (Feb.) 1923.

20 Holmes, W., and Ranson, S. W. Cervical Sympathectomy in Angina Pectoris, *J Lab & Clin Med* **10** 183 (Dec.) 1924.

21 Levy, R. L. Cardiac Pain. A Consideration of Its Nosology and Clinical Associations, *Am Heart J* **4** 377 (April) 1929.

22 Labat, G. Regional Anesthesia. Its Technique and Clinical Application, Philadelphia, W. B. Saunders Company, 1922.

23 Swetlow (footnote 7, first reference).

at an angle of 45 degrees, it was then pushed in 2 cm farther. In the early cases, a water manometer was connected with the needle, to ascertain whether the tip was within the pleural cavity. If oscillations corresponding to respiration were observed the needle was withdrawn and reinserted. Next 5 cc of a 1 per cent solution of procaine hydrochloride was injected through each needle. After an interval of ten minutes 5 cc of an 80 per cent solution of alcohol was injected through each needle, and as soon as injection was completed, the needle was withdrawn.

According to White¹ the injection of 5 cc of alcohol causes the development of an area of necrosis followed by fibrosis, that is only about 1 cm in diameter whereas 5 cc of procaine hydrochloride diffuses over a somewhat wider area. In order to infiltrate with alcohol the regions through which the ram communicans pass it is clearly imperative that the injections be made accurately. The procedure is relatively simple but it requires practice on the cadaver.

REPORTS OF PERSONAL CASES

Case 1—History—Nelson Z., aged 36, a baker, was first seen in the Cardiac Clinic on April 16, 1928. He had been remarkably well up to the onset of the present illness. In August, 1928 (eight months previously), while walking home from work, he had a sudden attack of pain in the left side of the chest which radiated to the left arm and was accompanied by a sense of choking and oppression. He fell on the street and had to be taken home. The pain persisted throughout the night and it was relieved the following morning by hypodermic medication. The patient remained in bed for three weeks. Another attack occurred in November, 1928, which again confined him to bed for two weeks. Since then, walking for even a short distance or any excitement induced an attack. He described the pain as burning on the inner aspect of the left elbow and traveling upward along the arm to the precordium. The patient also had attacks of pain at night. Inhalation of amyl nitrate afforded relief. He had been unable to work for eight months.

Examination—On examination the heart was found to be slightly enlarged to the left. The rhythm was regular. The sounds were rather weak and had a feeble quality, but a gallop rhythm was not heard. The blood pressure was 134 systolic and 86 diastolic. An electrocardiogram showed inversion of T₁ and notching of R. A teleroentgenogram of the heart showed moderate enlargement with tortuosity of the aorta and prominence of the knob. The diagnosis was arteriosclerosis, coronary sclerosis, dilatation of the aorta and old coronary thrombosis, with a healed myocardial infarct.

Operation—The patient was admitted to the hospital on May 6, 1929. He was kept in bed for two weeks, during which he had several mild attacks of pain. He was then allowed to be up and about the ward for a week, and his symptoms increased. A paravertebral injection of alcohol was made on May 31, 1929. There was slight discomfort during the operation, and at its conclusion he was in good condition. Horner's syndrome (miosis, ptosis and enophthalmos) was not noted.

Postoperative Course—On the evening after the operation was performed, the temperature rose to 101.2 F and the heart rate to 110. On the following day the temperature was 101.8 F, and a slight elevation ranging from 100 to 101.2 F persisted for ten days. Tachycardia was present for only three days. On the

day of injection the blood pressure was 145 systolic and 95 diastolic. On the next day it was 105 systolic and 75 diastolic, and then it gradually resumed its former level. There were slight variations in the degree of inversion of T_1 and in the location of the notch in R_3 , but these were not striking. The sensory disturbances are shown in the accompanying chart (fig 2). The patient vomited once and complained of severe headache. He complained of pain in the left side of the chest, which was aggravated by respiration. In the course of a week almost complete anesthesia of the skin corresponding to the first five thoracic segments, in front and in back, was observed. He continued to complain of pain in the upper part of the left side of the chest, but there was no recurrence of the original

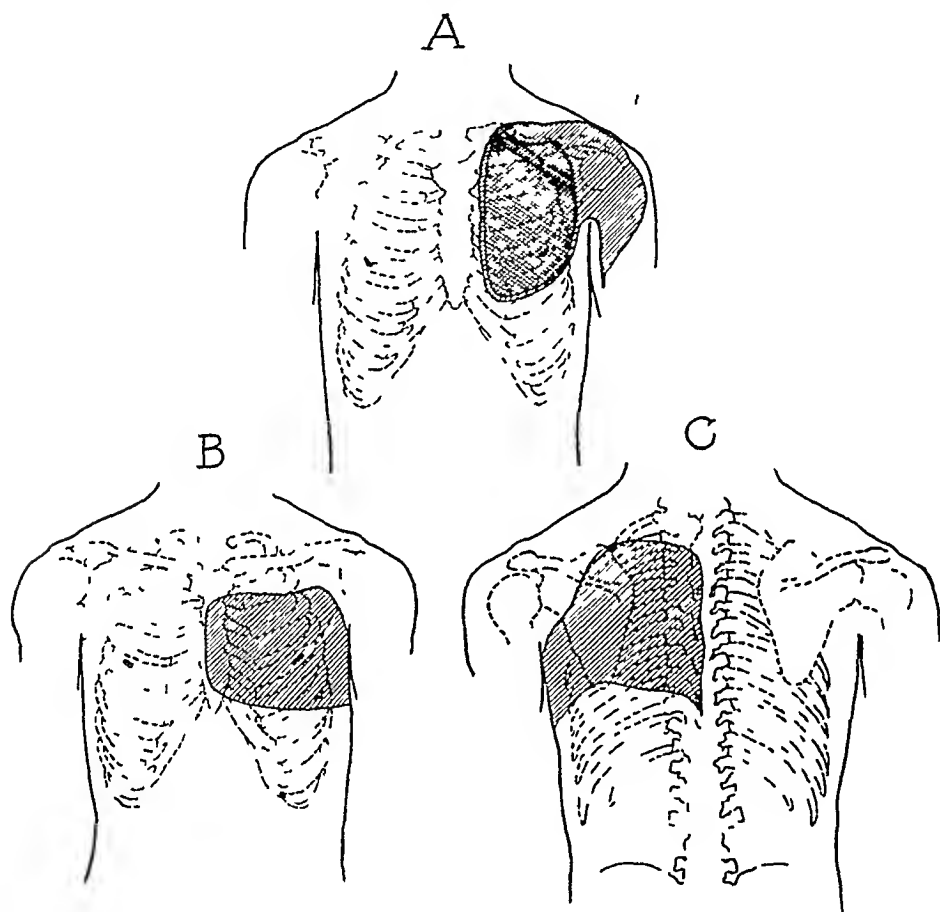


Fig 2—Sensory disturbances in case 1. *A*, before injection. The single cross hatching denotes hyperesthesia to touch and pain, the double hatching, hyperesthesia to heat and to cold. *B* and *C*, one day after injection of the first five dorsal rami. The hatched areas denote hypesthesia to touch, pain, heat and cold.

attacks. On June 19, he walked briskly four times the length of the hospital corridor without discomfort.

The patient was seen at frequent intervals. For six weeks, he continued to complain of pain in the region of the injections, which radiated around the chest to the front, but the precordial discomfort never recurred. There was a slight "substernal heaviness" on walking rapidly. On November 18 (six months after injection), he returned to his work as a baker. His employer excused him from lifting heavy sacks of flour. At this time the heart rate was 90, and the

rhythm was regular. The blood pressure was 142 systolic and 96 diastolic. In March, 1930 (ten months after injection), he complained of dyspnea on walking in the street. He was given a course of digitalis, with much benefit. The last follow-up was on October 2, sixteen months after the injection. He had experienced no pain but he still became slightly short of breath on walking rapidly. He was working regularly as a baker.

CASE 2—History—Benjamin B., aged 54, a hatmaker and porter, was known to have had diabetes for at least three years. He first noticed cardiac pain in 1925, four years before examination. The attacks were precordial and radiated to the left shoulder and down the left arm; they were definitely related to exertion. During the attacks he became dyspneic and sweated profusely. The diabetes was satisfactorily controlled. Over a period of three years, various therapeutic measures were tried for relief from pain including deep roentgen therapy administered to the chest but there was no improvement and he was unable to work.

Examination—The patient was admitted to the hospital on Oct. 23, 1929, for the paravertebral injection of alcohol. The diagnosis was diabetes mellitus, arteriosclerosis with coronary involvement and cardiac hypertrophy. The heart was moderately enlarged. The cardiac rhythm was regular, and the sounds were of moderate intensity. The blood pressure was 135 systolic and 74 diastolic. The Wassermann reaction of the blood was negative. The electrocardiogram showed no significant changes. Roentgenograms of the legs showed calcification of the blood vessels.

Operation and Course—A paravertebral injection of alcohol was given on October 29. The patient complained of mild local discomfort at the time of injection. Horner's syndrome did not develop. On the day following injection, the temperature rose to 102.2 F. and the heart rate to 108. There was a slight elevation in temperature for five days. Afterward both fever and tachycardia subsided. The patient complained of great pain in the left side of the back at the site of injection, particularly on moving the left arm. There was a small area of hyperesthesia and sensitivity to cold on the left side of the neck, which extended from the chin to the angle of the jaw. There was no recurrence of the attacks. Ten days after injection, he again complained of substernal and precordial pain, chiefly at night; it was sometimes associated with nausea and vomiting. It was not like the pain from which he formerly suffered. Three weeks after injection he experienced his first attack of precordial pain, which shot down the left arm and caused numbness of the index and middle fingers of the left hand. He was still in bed at this time. He was discharged from the hospital on November 22, three and one-half weeks after the injection. At this time he was free from cardiac discomfort. There were no changes in the form of the electrocardiogram.

On December 18 he was still experiencing cardiac pain, but his condition was better than before injection. On Jan. 13, 1930 (two and one-half months after injection), he stated that the attacks were recurring and the dyspnea was increasing. At this time, it seemed probable that gradual arteriosclerotic closure of the left coronary was taking place.

Readmission to Hospital—The patient was readmitted to the hospital on January 13, because of a recurrence of the pain in the left side of the chest. He looked poorly. The blood pressure was 145 systolic and 70 diastolic. There was still hyperesthesia and pain in the area supplied by the injected ram communicans. It appeared likely that complete degeneration of the nerve roots had not occurred and that the painful phenomena were due to persistent irritation. Re-injection was advised but refused. The attacks now were not relieved by glyceryl

trinitrate The patient became dizzy and somewhat confused mentally, so that it was difficult to estimate the degree of suffering The duration of follow-up was only four months On February 11, it became necessary to transfer him to another hospital for permanent care It was thought that the cerebral symptoms were due to progressive arterial changes The patient was afforded complete relief for about three weeks and partial relief for three months

CASE 3—History—Sarah Z, aged 68, a Polish housewife, was admitted to the hospital on April 19, 1929 She had had pneumonia six years before, which was followed by an abscess in the left hip that had resulted in shortening of the leg Cholecystectomy had been done twenty-five years previously Diabetes was discovered during the course of pneumonia For twenty-five years, she had noted dyspnea on exertion, together with cramplike pain in the precordia Lately the pain had radiated to the left arm Glyceryl trinitrate afforded relief An attack lasted for as long as an hour Recently she had noted swelling of the ankles, and she was obliged to sleep on several pillows

Examination—The patient was obese The lungs were emphysematous The heart was slightly enlarged to the left, and roentgen examination showed that the aortic knob was prominent The heart sounds were rather weak, and there was a systolic blow at the apex The rhythm was regular The blood pressure was 140 systolic and 75 diastolic The electrocardiogram showed only slight left ventricular preponderance The diagnosis was diabetes mellitus and coronary sclerosis

Course—The diabetes was readily controlled While in bed in the ward, the patient had several severe attacks of pain, which radiated to the neck and down the inner side of the left arm and lasted from ten minutes to one-half hour She cried, perspired and tossed about During the attack the blood pressure rose to 230 systolic and 130 diastolic Amyl nitrite and glyceryl trinitrate afforded only slight relief, and morphine was necessary to make her comfortable There was an area of marked hyperesthesia to pain, touch, heat and cold, covering the left side of the head, the neck, the left side of the chest and the abdomen, in front and in back The area of greatest intensity was in the lower part of the precordia and the left axilla and to a lesser degree over the left temple and in the region of the left mandible

Operation—On June 15, a paravertebral injection of alcohol was given The patient stood this procedure very well She experienced severe pain in the precordial region when alcohol was injected into the second dorsal root On the day following operation, the temperature rose to 100.4 F and the heart rate to 112, but next morning both the temperature and the pulse rate were normal For two days there was moderate pain at the site of the injections, radiating around the left side of the chest Five days after the injection, she awoke suddenly with a choking sensation and pain in the precordia, which radiated to the shoulder, the left side of the jaw and into the arm During the attack, the blood pressure was 164 systolic and 104 diastolic Inhalation of amyl nitrite gave no relief, but morphine made her comfortable She had another attack on the tenth day after operation, and again on the twelfth, each time with elevation of blood pressure During the height of the last attack the blood pressure was 210 systolic and 150 diastolic She stated that it felt as though the heart were being "squeezed like a ball" She was discharged from the hospital on June 28

Postoperative Course—The patient was seen on September 30 (three months after injection) Her daughter stated that she had not had an attack for seven weeks, and that "she was a different woman since the operation" The patient,

however, maintained that she was still having pain, which began in the ring finger and the little finger of the left hand, traveled up the arm to the neck and terminated in a sense of substernal oppression with choking. The pain was unrelated to effort. Walking rapidly or going up stairs caused dyspnea, and she felt that she was not improved. The blood pressure was 158 systolic and 94 diastolic. The heart rate was 92. The heart sounds had a tic-tac, valvular quality. There was slight edema of the ankles and legs.

Readmission—The patient was readmitted to the hospital on November 12, because of a recurrence of the cardiac attacks, symptoms of cardiac insufficiency and asthma. The paroxysms recurred while the patient was in the hospital, and she became irrational and violent. It was thought that the mental disturbance was due to progressive cerebral arteriosclerosis. On December 11 (seven months after injection), she was transferred to a psychopathic hospital. In this case there was probable partial relief for seven weeks, followed by recurrence of the attacks.

CASE 4—History—Samuel L., aged 35, a cutter of boxes, was first seen in the Cardiac Clinic on Feb. 19, 1930. He had had rheumatic pains and swelling of the joints at intervals for four years, which on one occasion had confined him to bed for a week. The present illness had begun eight weeks previously with substernal pain, which radiated upward symmetrically to both sides of the chest and the neck and to the jaws. On one occasion, there was radiation to the right arm below the elbow. The attacks were induced by slight effort and lasted from a few minutes to several hours, they were only slightly relieved by glyceryl trinitrate. The patient was unable to work at his trade because of discomfort.

Examination—The patient was rather pale, but there was no dyspnea or cyanosis. The heart was not enlarged, the rhythm was regular, and the sounds were of good quality. There was a short systolic blow at the apex and at the aortic area. The second aortic sound was slightly accentuated. The blood pressure was 142 systolic and 98 diastolic. There were numerous carious teeth, and the tonsils appeared to be badly infected. An electrocardiogram showed well marked left ventricular preponderance and diphasic T waves in leads 1 and 2. A teleoroentgenogram of the heart showed slight cardiac enlargement due to prominence of the left ventricle. The Wassermann reaction of the blood was negative. The diagnosis was coronary sclerosis, chronic tonsillitis and dental caries.

The patient was admitted to the hospital on February 26. The infected teeth were removed. Tonsillectomy was performed on March 28. In taking daily electrocardiograms, it was interesting to note slight variations in the T wave, particularly in lead 1. This wave changed from the inverted to the upright position, although no drugs were given that could have modified its form. On April 7, the patient reported that he had had no pain or discomfort since leaving the hospital, although he lived up two flights of stairs, however, on April 21 (two weeks later), he returned to the clinic, stating that he was again very uncomfortable. Walking induced severe pain and caused him to "crumple up." The discomfort was more intense than before. The pain was substernal and radiated around the axilla to the left scapular region and to the left arm. He was unable to work, and he was readmitted to the hospital on April 22. Even with rest in bed, a sense of pressure persisted in the region of the heart, although there was no acute pain. Lumbar puncture yielded normal fluid that gave a negative reaction to the Wassermann test.

On April 29, a paravertebral injection of alcohol was given. The patient complained of the usual amount of discomfort, but he did not cough or manifest any evidence of respiratory embarrassment. On May 1, two days later, he complained of sharp pain in the left side of the chest on inspiration. The temperature was 101.2 F. There were signs of fluid at the base of the left pleural cavity, which was confirmed by roentgen examination. The horizontal level of the fluid suggested to Dr. Reeves atelectasis of the lower part of the left lobe, but pneumothorax could not be seen in the upper portion of the lung. At this time the leukocytes numbered 9,400, 53 per cent of which were polymorphonuclears. The signs of fluid disappeared in the course of a week. There was a slight elevation of temperature to 100.4 F. for five days. The patient was sent home on May 10, twelve days after the injection of alcohol. He was free from pain of cardiac origin, but he complained of discomfort in the region of the injection and in the axilla.

Course—The patient was next seen on May 26 (four weeks after injection). He still complained of intercostal pain and discomfort on breathing, the latter symptom was relieved by the placing of a tight band around the thorax. He stated that this pain was not the same kind as that which he had experienced before the injection was made. On June 9 (six weeks after injection), he still had some discomfort over the left side of the chest, the pain was constant, but it was aggravated by walking. He said that it "felt more like the pleurisy pain." He was gaining weight and feeling better. The blood pressure was 118 systolic and 82 diastolic. On June 30 (two months after injection), he said that he was feeling wonderfully well. He was entirely free from pain, and he could walk six or seven blocks slowly without discomfort and was ready to take a light job. He failed to report for further observation, and attempts to locate him were unsuccessful.

In this patient, pleural effusion was observed following the paravertebral injection of alcohol. At the same time there was fever but not leukocytosis. There were the usual radicular pain and hyperesthesia, but complete relief from the attacks of cardiac pain was obtained.

CASE 5—History—Harris C., aged 48, a restaurant keeper, was admitted to the hospital on March 22, 1930, complaining of precordial pain and dyspnea on exertion for the past nine years. He had had scarlet fever as a child, but otherwise he had been well. The present illness had begun nine years previously with pain in the left arm, which occurred in cold weather and was relieved by warmth. Within a short time, pain began to spread to his heart, and at times he noted it beneath the left eye. For the past five months he had become definitely worse. The pain was related to exertion and was relieved by nitrites. Recently, it had radiated to the shoulder, down the left arm and often to the neck, both sides of the face and the teeth. At times attacks occurred at night. During the preceding five months he had been totally incapacitated, and he had lost 35 pounds (15.9 Kg.).

Examination—Examination showed slight cardiac enlargement to the left. The rhythm was regular. The sounds were rather weak. There was no accentuation of the aortic second. The blood pressure was 142 systolic and 70 diastolic. The electrocardiogram showed only left ventricular preponderance. The Wassermann reaction of the blood was negative. The basal metabolic rate was +12 per cent. The diagnosis was coronary sclerosis and cardiac hypertrophy.

The patient was discharged on March 28, but he was readmitted on April 14 because of the persistence of symptoms. He was taking about ten tablets of

glyceryl trinitrate during the day and using two amyl nitrite pearls at night. Walking for a distance of one-half block caused dyspnea. He was an absolute invalid, and was willing to submit to any procedure for relief.

An injection of alcohol was given on April 17. The operation went smoothly, and there was no complaint of discomfort. On the day following injection, the temperature rose to 103 F and the heart rate to 128, and he had a sharp chill. He complained of severe pain in the left side of the chest, he coughed occasionally and said that the pain was aggravated on taking a deep breath. There were signs of fluid in the left pleural cavity. There was also definite hypesthesia of the left side of the chest, in front and in back, together with a well marked Horner's syndrome. Fluoroscopic examination of the chest showed a small amount of fluid in the left costophrenic angle. The leukocyte count was 11,600, with 86 per cent polymorphonuclears. On the second day following injection the temperature was 101.6 F, the heart rate, 120. The blood pressure was 124 systolic and 72 diastolic. The pain on respiration was less marked.

Course—During the following week the effusion in the left pleural cavity was absorbed. The patient complained that the left side of the chest felt dead. The temperature returned to normal on the fourth day. The patient was allowed to get up gradually. There was no return of cardiac pain, but a sense of pressure over the precordia persisted. He was seen on May 19, and again on June 2, the latter date being six weeks after injection. The pain was not as severe as before, but he still had nocturnal attacks. Any exertion caused dyspnea and pressure over the lower part of the sternum, together with a choking sensation. The arm hurt when he moved it, and there was a tender spot below the left nipple. The functional capacity was unchanged, although there was some modification of the character of the symptoms. He was unable to do any kind of work, and he felt that he had been little benefited by the injection. During the following three months, he was almost entirely free from pain. The attacks then recurred, and on October 6 (six months after injection), the condition was essentially as when the patient was first seen.

CASE 6—History—Abraham G., aged 68, a retired Austrian Jew, had been observed in the outpatient department since October, 1924, and he had received treatment for diabetes mellitus and syphilis. He was admitted to the hospital on Feb. 5, 1930, because of pain in the precordia. This pain had been present for about eight years. It was almost constantly present as a dull ache and a sense of oppression, but it was aggravated by any exertion. There was no dyspnea or edema.

Examination—The heart was slightly enlarged. The rhythm was regular, the sounds were of fairly good quality. There was no gallop rhythm and no accentuation of the second aortic sound. The peripheral vessels showed moderate thickening. The lungs were emphysematous. The blood pressure was 165 systolic and 60 diastolic. The Wassermann reaction of the blood was 4 plus. There were no signs of aortitis. The electrocardiogram showed slight left ventricular preponderance. The diagnosis was coronary sclerosis, diabetes mellitus, emphysema of the lungs and syphilis.

Operation—An injection of alcohol was given on February 12. The patient complained of considerable discomfort during the injection, but he was in good condition at the termination of the operation. On the day following injection, the temperature rose to 101 F and remained elevated for eight days. There was also moderate tachycardia, and the heart rate ranged from 88 to 104. Following the injection the patient complained bitterly of pain in the back, radiating around

the side of the chest. It was difficult to gage the severity of the symptoms, as he was a highly nervous person who varied his story from day to day. He left the hospital on March 2.

Course—On March 10 (one month after injection), the patient stated that the substernal pain was somewhat less severe, although he had had an occasional twinge just to the right of the midline. The pain at the site of the injection was intense and constant, and he stated that he was unable to sleep. It appeared that the pain of cardiac origin was partially relieved, but that neuritis was still causing considerable discomfort. On October 6 (seven and one-half months after injection), he stated that he was no better than before operation. This case must be considered a therapeutic failure. Antisyphilitic treatment was resumed.

CASE 7—History—Anna W., aged 50, a Polish housewife, was admitted to the hospital on March 12, 1930. She had been complaining of pain in the region of the heart for three and one-half months. Pain began suddenly while she was walking and radiated from the precordial region to the inside of both arms, to the ears and to the gums. The pain was very severe, and it was accompanied by weakness, palpitation and fear of death. The first attack lasted only a few minutes, but several twinges occurred that night while the patient was in bed. After a free interval of two weeks, discomfort returned, and for three months she had been completely incapacitated. The pain occurred particularly on exertion, but also at rest. Nitrites afforded some relief. There was no dyspnea or edema.

Examination—The patient was slightly cyanotic. The heart was moderately enlarged. The sounds were clear and of fair quality. There was a musical systolic blow at the apex. The second aortic sound was hollow and slightly accentuated. The blood pressure was 160 systolic and 100 diastolic. The electrocardiogram showed inversion of T_1 . The Wassermann test of the blood gave a negative result. The diagnosis was coronary sclerosis, hypertension and fibrosis of the myocardium. There was slight hyperesthesia to pressure in a localized area around the left nipple and over the left scapula. While she was in the ward, the patient continued to experience pain, even at rest.

A paravertebral injection of alcohol was given on March 27. The patient cooperated well, and there was no pain during the injection. On the following day, a definite Horner's syndrome was present. There was no cardiac pain and only slight tenderness over the site of injection. The temperature on the second day rose to 101.6 F and the heart rate to 96. On the following day, the temperature was 102 F and on the fourth day 101.6 F. At the end of a week the temperature was still 100 F in the evening. Hypesthesia developed over the left side of the chest, in front, in back and in the axilla. As a result of the injection of alcohol, the pains in the precordia, the left arm and the left side of the neck disappeared. However, the patient continued to have attacks of moderate pain under the sternum, on the inner side of the right arm and in the right side of the neck. These attacks were accompanied by a definite rise in blood pressure, frequently to 200 mm of mercury.

On the tenth day after injection, the patient complained of more intense pain, and the temperature rose to 102 F. The leukocyte count was 16,300, with 86 per cent polymorphonuclears. An electrocardiogram taken two days later showed that right bundle branch block had developed, with the usual marked inversion of T_1 . This combination of observations afforded good evidence that coronary thrombosis had occurred, with infarction of the left ventricle. The patient complained of severe pain in the region of the apex, in the midsternal region and in

the right arm. She continued to have attacks and became unstable emotionally. Gradually, she began to improve and was finally able to sit in a chair.

It was difficult to estimate the severity of the pains, as she described them poorly and was always anxious and complaining. She was discharged on June 6, two and one-half months after injection. In this case, the picture was complicated by acute coronary obstruction. In spite of this occurrence, it should be noted that she was free from pain on the left side, but complained of substernal discomfort, radiating to the right arm.

On July 30 (four months after injection), she reported that there had been no recurrence of cardiac pain, though at times palpitation was annoying. She complained of a constant dull ache in the shoulders and arms, which was probably of neuritic origin, since roentgen examination revealed well marked arthritis of the cervical vertebrae. She was able to walk about the house and to go motoring. At this time the blood pressure was 210 systolic and 135 diastolic.

CASE 8—History—Arthur S., aged 58, an architect, was admitted to the hospital on March 7, 1930, complaining of paroxysmal pain in the sternal region and the epigastrium of five years' duration. The present illness began suddenly, when he was awakened early one morning by a terrific epigastric pain, sharply localized. This pain was relieved by a hypodermic injection. Shortly thereafter, while hurrying for a train, the pain recurred and made him stop. The attacks then increased as time went on and the amount of effort which he could make was greatly limited. During the early attacks, the pain had radiated to both arms, and it had been worse on the right side, but lately radiation was less marked. There had been no dyspnea or edema. For eight months, he had spent almost all of his time in bed. The slightest effort induced discomfort and he had a number of attacks while bedridden. He also suffered considerably from gaseous distention and constipation. The pain was always relieved by glyceryl trinitrate.

Examination—Examination showed several badly infected teeth, which were promptly removed. The heart was not enlarged. The aorta was tortuous but not dilated, as shown in the roentgenogram. The blood pressure was 145 systolic and 80 diastolic. The electrocardiogram showed diphasic T_2 and sharply inverted T_3 , together with notching of R . Roentgenograms of the gastro-intestinal tract showed a small duodenal ulcer, but there was no blood in the stools. The diagnosis was coronary sclerosis and duodenal ulcer. The ulcer appeared to be playing a minor rôle in the production of symptoms. However, the patient was put on a Sippy regimen for ulcer.

Operation—On March 19, a paravertebral injection of alcohol was given. When the injection was made into the fourth thoracic root, the patient exclaimed, "That caused a pain in my heart just like the ones I always have." Injection into the other roots was unattended by discomfort. The procedure was well borne. Horner's syndrome did not appear. The patient had two attacks on the night following injection, but there was no fever or tachycardia at any time. On the third day, an area of anesthesia was noted in the back, over the lower portion of the scapula and in the left part of the midscapular and subscapular regions. There was no anesthesia in the axilla or in front. He continued to have mild attacks of pain, which were always relieved by the taking of glyceryl trinitrate, but these attacks occurred less frequently, and they were less disturbing. He left the hospital on April 19, as an ambulatory patient, one month after injection.

Course—He was again seen on July 1 (three and one-half months after injection). He continued to have a sense of soreness in the upper part of the left

TABLE 1—*Paravertebral Injections of Alcohol Detailed Analysis of Thirty-Seven Cases*

Author	Case	Location of Pain	Duration of Attacks	Age and Sex	Diagnosis	Site of Injection*	Result	Degree of Relief	Length of Follow Up	Horner's Syndrome?	Comments and Last known Status
Swetlow (Am Heart J 1: 393, 1926)	1	Precordial, radiating to left shoulder blade and down left arm, induced by slight effort	2 yr	20 F	Syphilitic aortitis, aortic insufficiency	4 7 DL	Marked, though incomplete relief	P	6 mo	?	Pain had persisted in spite of specific therapy, able to carry on increased activity, still having short fleeting pains
	2	Retrosternal, penetrating anteroposteriorly, induced by effort	10 mo	63 M	Coronary sclerosis	3 7 DL 1 1 DL	Complete relief within 24 hours	C C	4 mo 6 mo	?	Relief lasted 4 months, then pain recurred, given second injection Again completely relieved, had slight retrosternal pressure at times
Swetlow and Schwartz (J A M A 86: 1679 1926)	3	Precordial and in left interscapular region, both after effort and at rest	15 mo	18 F	Mitral stenosis and insufficiency cardiac insufficiency	3 9 DL	Moderate relief while in bed	P	3 mo	?	Some pain persisted, died 3 months later of cardiac insufficiency, 60 per cent solution of alcohol used for injection
	4	Precordial, on effort and in bed, at night	4 yr	61 M	Coronary sclerosis, coronary and cerebral thrombosis	1 2 DL	Marked relief	P	8 mo	?	Almost complete relief, dyspnea and cyanosis on effort
Swetlow (Am J Surg 9: 88, 1930)	5	Precordial, radiating to left arm, on effort and in bed	2 yr	65 M	Coronary sclerosis	2 5 DL	Pain disappeared	C	2 mo	?	Pulmonary edema and dyspnea recurred, died suddenly after 2 months
	6	Precordial, radiating down left arm, on effort or at rest	6 yr	72 M	Coronary sclerosis	1 5 DL	Great relief	P	3 mo	?	Occasional fleeting precordial pain, able to increase activity, general condition improved because of relief from suffering
7	7	Paroxysmal, on effort or at rest	3 yr	60 F	Coronary sclerosis	1 9 DL	Complete relief of pain, though cardiac insufficiency persisted	C	6 days	?	Critically ill, died suddenly 6 days after injection
	8	Precordial, radiating to left arm, on effort and at night	5 yr	62 M	Coronary sclerosis	1 9 DL	Great relief	P	4 mo	?	Attacks of pain mild and fleeting, comfortable

White and White (J A M A 90 1059, 1928)	1	Left side of chest, radiating down left arm, on slight effort	3 yr	54 M	Syphilitic aortitis, aortic insufficiency, hypertension, confined to bed	1 5 DL	Complete relief of left sided attacks, recurrence of pain on right side	O (100%)	13 mo	+	Attacks increased in frequency and severity in spite of specific therapy, second injection for attacks on right side
Richardson and White (Am J M Sc 177 161, 1929)						1 5 DR	No relief of right sided attacks	0			Up and about, still having right sided pain and occasionally substernal discomfort, unable to work
						1 5 DR	Improved	P (75%)	3 yr		After third injection, rare right sided pain, no left sided pain
White (Ireh Neurol & Psychiat 22 304, 1929, Am J Surg 9 98, 1930)	2	Substernal, radiating to interscapular region	4 yr	60 M	Coronary sclerosis, aortic insufficiency, hypertension	2 6 DL	Relief for 2 weeks	P (slight)	5 wk	+	Pain recurred, had second injection after 5 weeks, attacks became milder
						1 3 DL	Pain milder	P (60%)	9 mo		Resumed light work, died of coronary thrombosis 9 months later
	3	Preordial, radiating down left arm	3 yr	53 F	Arteriosclerotic heart disease, hypertension	1 5 DL	Recurrence of pain after 6 days, little improvement	P (25%)	2 1/4 yr	0	Still having several attacks each day, a nervous woman, up and about, painful hyperesthesia and paresthesia after injection, died of empyema after 2 1/4 years
	4	Substernal, radiating to both arms, worse on left	4 yr	54 M	Arteriosclerotic heart disease	1 5 DL	Left sided relief, still had right sided attacks	P (100% on left)	2 1/2 yr	+	Pleural pain after injection, left sided pain relieved, still had pain on right and dyspnea, resumed work as truck driver for 3 months, now having dyspnea
	5	"Typical angina"	1 yr	59 M	Arteriosclerotic heart disease, hypertension, coronary thrombosis	1 5 DL	Partial relief	P (40%)	4 mo	0	Pain less severe, but dyspnea increased, died suddenly 4 months later
	6			52 M	Hypertension, aortic insufficiency	1 5 DL	Complete relief at first, later slight recurrence	P (90%)	2 1/4 yr	?	Comfortable and able to do light work
	7			58 M	Arteriosclerotic heart disease, hypertension	1 5 DL	Considerable relief	P (65%)	5 mo	?	Resumed light work, comfortable
	8			68 M	Arteriosclerotic heart disease, hypertension, previous coronary thrombosis	1 5 DL	Partial relief at first, then recurrence	P (50%)	10 mo	?	Up and about, but having daily attacks, died after 10 months of coronary thrombosis

* D indicates dorsal, O, cervical, R, right, I, left
+ C indicates complete, P, partial

TABLE 1—*Paravertebral Injections of Alcohol Detailed Analysis of Thirty-Seven Cases—Continued*

Author	Case	Location of Pain	Duration of Attacks Age and Sex	Diagnosis	Site of Injection*	Result	Degree of Relief† Follow Up	Length of Syn- drome	Comments and Last Known Status
	9		47	Coronary sclerosis and thrombosis, hypertension	1 5 DL	Attacks relieved	C (100%)	2 mo	Died of cardiac insufficiency 2 months later, had right sided pain
	10		51	Arteriosclerotic heart disease, coronary thrombosis morphism	1 5 DL	Relief until death	—	5 days	Another attack of coronary thrombosis 5 days later, died 3 weeks after injection
	11		56	Arteriosclerotic heart disease hypertension	1 3 DL	Complete relief for 4 mo, then slight recurrence	C and P (100 90%)	7 mo	Worked for 4 months, apoplexy, few mild attacks for 2 months
	12		57	Arteriosclerotic heart disease, hypertension, coronary thrombosis	1 4 DL	Much improved	P (90%)	4 mo	Returned to light work, rare attacks
	13		56	Arteriosclerotic heart disease, coronary thrombosis	1 3 DL	Complete relief	C (100%)	3 mo	Continued to practice medicine
	14		54	Arteriosclerotic heart disease, coronary thrombosis	1 4 DL	Complete relief	C (100%)	2 wk	Followed only 2 weeks
	15		49	Arteriosclerotic heart disease	1 3 DL	Much improved	P (75%)	3 mo	Planned to return to work
	16		57	Arteriosclerotic heart disease	1 1 DL	No relief	0	?	Condition as before injection
	17		52	Syphilitic aortitis	1 4 DL	No relief	0	?	Condition as before injection
	18	Upper right portion of chest and neck		Syphilitic aortitis aneurysm of ascending aorta	1 2 DR	Complete relief	C (100%)	3 mo	Comfortable until death 3 months later, due to rupture of aneurysm
Sprague and Mixer (New England J. Med. 200 199, 1929)	1	Substernal	10 yr M	Coronary sclerosis and thrombosis, hypertension, obesity	1 5 DL	One mild attack 1 week after injection, then complete relief until death	C (100%)	2 mo	Continued to have cardiac asthma progressive cardiac failure terminated in death 2 months later, at operation, pain relieved after injection of third and fourth dorsal nerves

Cattell and Hursthal (J A M A 92 1510, 1929)	1	Substernal and precordial, radiating down left arm	1 mo	32 M	Coronary sclerosis	8 O { L 1 5 D }	Only occasional twinges for 5 mo., (40% for then coronary thrombosis and recurrence	P (40% for 5 mo)	8 mo	+	Worked for 5 months, then again inapaetated after attack of thrombosis
Levy and Moore	1	Left arm, traveling to precordium	8 mo	36 M	Coronary sclerosis	1 5 DL	Pain entirely relieved	C	16 mo	0	Radicular pain for 6 weeks, some dyspnea on effort, at work, at his trade of baker, no cardiac pain
	2	Precordial, radiating to left shoulder and arm	4 yr	54 M	Coronary sclerosis, diabetes mellitus	1 5 DL	Complete relief for 2 weeks, then recurrence	P	4 mo	0	Great deal of radicular pain after operation, final result obscured by symptoms of cerebral arteriosclerosis, partial relief for 3 months
	3	Precordial	25 yr	68 F	Coronary sclerosis, diabetes mellitus	1 5 DL	Relieved for 7 weeks	C (7 wk then 0)	7 mo	0	Relief at first, then recurrence, psychosis developed so that final result is in doubt
	4	Substernal, radiating to both sides of chest, to neck and jaws	8 wk	35 M	Coronary sclerosis	1 5 DL	Complete relief	C	2 mo	0	Pleural effusion developed after injection, disappeared from observation
	5	Precordial, radiating to left arm, in left eye	9 yr	48 M	Coronary sclerosis	1 5 DL	No pain for 3 mo., substernal oppression persisted	C (tempo rary)	6 mo	+	Pleural effusion developed after injection, free from pain for 3 months, recurrence, never relieved from substernal oppression
	6	Precordial	8 yr	68 M	Coronary sclerosis, diabetes mellitus, syphilis	1 5 DL	Slight relief for 1 month, then recurrence	0	7 1/2 mo	0	Severe radicular pain, slight temporary relief, a therapeutic failure
	7	Precordial, radiating to arms, ears and gums	3 1/2 mo	50 F	Coronary sclerosis, coronary thrombosis	1 5 DL	Left sided relief for 10 days, pains under sternum and on right for a time, then complete relief	C	4 mo	+	Coronary thrombosis 10 days after injection, recovery, followed by persistent, though less severe pain for a time, then complete relief
	8	Substernal and epigastric	5 yr	58 M	Coronary sclerosis, duodenal ulcer	1 5 DL	Attacks much milder and less frequent	P	8 mo	0	Greatly improved, after having spent 8 months in bed, he is now up and about, carrying on a fair amount of activity
	9	Substernal and precordial	2 yr	47 M	Coronary sclerosis	1 5 DL	Attacks milder but still present	P	6 mo	+	Partial relief, a person of meager intelligence

axilla, although it was not tender on deep pressure. The cardiac pain was much less frequent and less severe. The worst attack usually occurred in the morning, after breakfast, while shaving or bathing. The pain was invariably relieved by glyceryl trinitrate. He was much stronger and more active, and he was able to take motor rides and to resume a certain amount of social activity. He felt that he had been tremendously benefited by the injection and that he was continuing to improve. Roentgenograms of the gastro-intestinal tract showed that the duodenal ulcer had healed. On November 3 (eight months after injection), he reported continued progress and planned to resume part-time work.

CASE 9—History—Max S., aged 47, a Russian machinist, was first seen in the Cardiac Clinic on March 26, 1930. He complained of attacks of substernal pain and dyspnea on exertion for the past two years. The pain was of a twisting and squeezing nature, and it radiated toward the left arm and hand. The attacks gradually became more and more easily provoked, and lately they had been localized to the upper part of the sternum and the precordia. Nitrites afforded relief. Two years before, he had been at another hospital, where a diagnosis was made of manic-depressive psychosis in the depressive stage. He had not worked for two years.

Examination—Roentgen examination showed moderate cardiac enlargement and moderate but diffuse dilatation of the aorta. The electrocardiogram showed inversion of T_1 and T_2 . The blood pressure was 230 systolic and 120 diastolic. There were no signs of cardiac insufficiency. The diagnosis was hypertension, coronary sclerosis and fibrosis of the myocardium.

Operation—On April 10, a paravertebral injection of alcohol was given. The patient was apprehensive and complained of some discomfort, but this was not severe and there were no manifestations of pleural irritation. On the evening of operation, the temperature rose to 101.2 F, and for a week thereafter it reached 100 or 100.2 F in the afternoon. A definite Horner's syndrome developed. The patient had slight soreness at the site of the injections. He stated that the anterior part of the chest felt dead. Objectively, there was hypesthesia over the distribution of the first five thoracic nerves on the left side, in front and in back. There was no recurrence of the paroxysms of pain during his stay in the hospital, from which he was discharged on April 22, twelve days after injection.

Course—The patient was seen on April 28 (eighteen days after injection). He had not used glyceryl trinitrate, but he stated that he had had pain in the back and over the precordial area. Horner's syndrome was still present, though less marked. The blood pressure was 224 systolic and 116 diastolic. There were occasional premature beats. Because of his depressed state, he was examined by a psychiatrist, who classified him as a constitutionally inferior individual. He was last seen on October 20 (six months after injection), and he still complained of pain all over the left side of the chest, together with a variety of other discomforts. It was almost impossible to appraise the degree of relief, because of the psychoneurotic state. The fact that he did not take glyceryl trinitrate indicated that he had been relieved at least in part. He did not seek work.

CLINICAL FEATURES

For detailed analysis, thirty-seven cases, including our own, are available, since Pletnew and Hesine¹³ reported only collective results and Swetlow²³ noted full data in but eight cases. In table 1 are given

the essential facts, and in table 2 these facts have been summarized. The series is small and the periods of observation are relatively short, so that an attempt to draw general conclusions at this time would be premature. Certain features are worthy of brief comment.

It appears that age, sex, the character of the pain and the duration of symptoms prior to injection did not materially influence the outcome. A preponderant majority of the patients were elderly persons, with arteriosclerosis and coronary involvement. A fair estimate of the degree

TABLE 2—*Paravertebral Injections of Alcohol: Summary of Thirty-Seven Cases in Which Data Were Available*

Number of injections		41
Left side	38	
Right side	3	
Etiologic type of cardiac disease		
Arteriosclerotic		32
Syphilitic		4
Rheumatic		1
Relief obtained		
Complete (49%)		18
Permanent	15	
(to death or last known status, 6 died within 6 months)		
Temporary	3	
Partial (43%)		16
Permanent	15	
Temporary	1	
None (8%)		3
Horner's syndrome		
Present		7
Absent		8
Not noted		22
Untoward effects		
Pleural effusion		2
Postoperative collapse		2
Bloody expectoration		1
Operative deaths		0
Duration of follow up		
Less than 6 months		20
6 to 12 months		12
1 to 2 years		1
2 to 3 years		4

of relief obtained may be made by averaging the results as recorded in forty-nine cases—twenty-two reported by Swetlow, eighteen from the Massachusetts General Hospital and nine of our own. Complete or almost complete relief was obtained in 51 per cent of the cases, improvement was noted in 34 per cent, and in 15 per cent the operation was a failure. According to these figures, then, 85 per cent of the patients have been benefited to some extent following injection. Even though the pain was not completely relieved, the attacks were described as milder and of less frequent occurrence. In some cases, relief was only slight and temporary, in others, the result was strikingly successful, as in case 1. Even partial relief, as in case 8, enabled the patient to return to limited activity, after having been confined to bed for most of the time during the eight months preceding operation. In one patient⁸

who received injections on the right side for dextral pain occurring after left-sided relief, a 75 per cent favorable effect was noted at the end of three years

Unsuccessful results are probably due in part to faulty technic, with failure to infiltrate the proper area, in part, perhaps, to conduction of pain impulses by other unknown pathways, and possibly, also, in a smaller measure, to individual anatomic variations in the nerves concerned. No patient has died as the result of the operation, although several were critically ill. Two died of coronary thrombosis within three weeks.

In fifteen cases, specific mention is made concerning the occurrence of Horner's syndrome, it followed injection in seven instances. In our series of nine cases, it was observed three times. White and White⁹ regarded this evidence of block of the upper dorsal sympathetic ramus as a favorable sign, but our experience has not led us to stress its importance.

Frequent electrocardiograms were made in our cases, but no changes were observed that could be directly ascribed to the effects of the injections of alcohol. Swetlow²⁴ reached a similar conclusion.

Any evidence throwing light on the particular nerve roots concerned in the mechanism of cardiac pain has been eagerly sought. It was with particular interest that we noted the remarks of two patients at the time of injection. As an injection was made into the second dorsal root in one instance, and into the fourth dorsal in another, each patient exclaimed, "That gave me a pain in my heart just like the ones I have always had." In three of the cases at the Massachusetts General Hospital, attacks of pain occurred while the patients were on the table. In one case, Spriague and Mixer⁹ observed that relief was promptly obtained after injections of alcohol were made into the third and fourth dorsal roots, whereas in the other two cases J. C. White²⁵ noted cessation of discomfort after injection was made into the third dorsal root. Pletnew,¹³ who gave injections into the first three or four dorsal ganglions and sometimes also into the seventh and eighth cervical ganglions, recorded two similar experiences. Several of his patients stated that "the needle felt as though it had pierced the heart", and from three to five minutes after injection, that "the heart disappeared." In one of his cases, while an injection was being made into the sixth and seventh cervical and the first three dorsal roots, signs of sudden cardiac weakness developed, for which strophanthin, camphor and caffeine were given. Multiplication of such observations should result in the accumulation of important data.

24 Swetlow (footnote 7, third reference)

25 White (footnote 12, first reference)

The discomforts and untoward effects of paravertebral injections of alcohol have not been sufficiently emphasized. A majority of the patients (eight of nine in our series) complained bitterly of pain and hyperesthesia in the cutaneous distribution of the nerve roots into which injections were made. Pain began within twenty-four hours, after the effects of the procaine hydrochloride had worn off, and it lasted, in some of our patients, for as long as six weeks. This form of discomfort, which was probably due to intercostal neuritis induced by the alcohol, is apparently unavoidable, though distressing and discouraging. In a few cases, diathermy seemed to afford some relief. A moderate degree of fever (from 100 to 102 F) was also observed in eight of our nine patients, and this symptom has been noted by others. This may persist for a week or ten days, and may well be due to necrosis of the tissues induced by the alcohol. Immediately following injection, and while still on the table, a patient of White and White⁸ complained of severe pain on the left side and of faintness. He became pulseless for thirty minutes, but recovered within an hour. It was thought that the reaction might be due in part to the intravenous injection of procaine hydrochloride, though the pain was believed to be of cardiac origin. Mixer¹¹ stated that he thought that in one case he put a little alcohol into the pleura. The pain was severe and markedly increased by respiration, and for a short time he "was much disturbed as to the outcome."

In two of our cases, pleural effusion developed on the left side, which was confirmed by roentgen examination. The effusions were small, and they were accompanied by considerable pain and fever, slight leukocytosis was found in one instance. It is curious that the patient did not complain of pain or respiratory distress at the time the injections were made. Therapeutic aspiration was not necessary, and the fluid was absorbed within a week. During the night following operation, one patient⁸ complained of mild pleural pain and raised some faintly blood-tinged sputum. In one of Swetlow's cases,²⁶ pneumothorax without effusion followed injection. Even with the utmost care in technic, the point of the needle rests very close to the pleural cavity. In the patients with effusion, it seems likely that the needle did not penetrate the pleura but caused irritation by contact of the alcohol with the outer surface.

In spite of these unpleasant and, at times, disturbing complications, the procedure of injection is comparatively safe in skilled hands. It has the disadvantage of being unaided by direct visual guidance. It is a measure designed to relieve pain, and it must clearly be understood that it does not, to the best of our knowledge, affect the basic pathologic state. Final judgment as to its value and limitations must be reserved until more cases have been observed over longer periods of time. For the present it should be employed only after carefully planned medical

26 Swetlow (footnote 7, fourth reference)

treatment has failed to alleviate intense suffering. Patients in whom pain has served as a danger signal of overexertion should be warned, if relieved of attacks, against exceeding the functional capacity of the heart.

SUMMARY

1 Based on fifty-seven cases reported in the literature and on nine that were personally observed, a critical analysis has been made of the results of paravertebral injections of alcohol for relief of cardiac pain.

2 The known facts concerning the nervous mechanisms involved in the transmission of cardiac pain have been briefly stated.

3 The technic of injection, as described, is relatively simple, but it requires skill acquired by experience on the cadaver. The procedure has the disadvantage of being unaided by visual guidance.

4 Of forty-nine cases in which adequate data are available, 51 per cent of the patients obtained complete or almost complete relief, improvement was noted in 34 per cent, and in 15 per cent the operation was a failure. Some patients were benefited only slightly and temporarily, in others the result was strikingly successful. In one personal case, there has been complete relief from pain for sixteen months.

5 After injection, a majority of the patients suffered from hyperesthesia of the wall of the chest and painful intercostal neuritis in the segmental distribution of the nerves into which injections were made. At times the discomfort lasted for as long as six weeks, and it was apparently unavoidable. Many patients had fever following injection, which lasted from a few days to a week. In two of our cases, effusion into the left pleural cavity followed the injections.

6 Horner's syndrome was observed in seven of fifteen cases in which notes on this point are available. Its occurrence did not afford an index of the ultimate therapeutic result. It tended to disappear in the course of several weeks or months.

7 Paravertebral injection of alcohol offers a reasonably good hope of some relief to patients with paroxysmal cardiac pain. Final judgment as to its value and limitations must be reserved until more cases have been observed over longer periods. For the present, it should be tried only after carefully planned medical treatment has failed to alleviate intense suffering. The procedure is relatively safe, and so far it has been unattended by operative fatality. The method has a sounder physiologic basis and is less dangerous than cervical sympathectomy.

8 This form of therapy is entirely symptomatic. So far as we know, the basic pathologic condition is unaltered. Patients in whom pain has served as a danger signal of overexertion should be warned, if relieved from attacks, against exceeding the functional capacity of the heart.

Book Reviews

DAS ULCUS PROBLEM IM LICHTE MODERNER RONTGENFORSCHUNG By PRIV DOZ DR H U ALBRECHT, Oberarzt der medizinischen Universitäts-Klinik, Frankfurt, a-M Paper Price, 10 marks Pp 79, with 110 illustrations Leipzig Georg Thieme, 1930

This monograph represents the result of combined clinical and roentgenologic study made on the subject of ulcer during a two year period. The author shows himself to be thoroughly familiar with the present-day trends in Germany, particularly with the anatomic studies of Konjetzny and the radiologic work of Berg. The study is divided into two phases, clinical and x-ray. The latter portion is excellently and adequately illustrated by means of films which emphasize the importance of the direct signs of ulcer.

During the period described, the author performed fluoroscopy on 1,527 patients with abdominal complaints of various kinds and found roentgen evidence of gastric or duodenal ulcer in 23.7 per cent. Ulcer was the most common abdominal lesion found. The ratio of duodenal to gastric ulcer was 58:1, the ratio of men and women afflicted was 80:99. Duodenal ulcer was found to be more frequent between the ages of 15 and 40, whereas gastric ulcer was somewhat more common after 40. The lesion apparently runs a more benign course in women than in men, hour-glass contracture of the stomach is more common in women. A familial story of ulcer was present in 21.2 per cent of the gastric lesions and in 30.5 per cent of the duodenal lesions. The author was unable to establish clear spring and autumn seasonal recurrences. He concludes by revising Moynihan's well known expression "In duodenal ulcer, the history is everything, the physical examination almost nothing" to read "In the diagnosis of peptic ulcer, the history and the x-ray are everything, the remaining clinical examinations almost nothing." The work is good, and it is carefully done. All students of gastro-enterology will find the book of interest.

A SYNOPSIS OF MEDICINE By HENRY LETHEBY TIDY, M A, M D, B Ch (Oxon), F R C P (LONDON), Physician to St Thomas's Hospital Fifth edition, revised Cloth Price, \$6 Pp 1,032, with index New York William Wood & Company, 1930

The general arrangement of the book follows that of Osler and McCrae's "Principles and Practice of Medicine," and the special arrangement of headings and types is on the same system as in Groves' "Synopsis of Surgery", the book was planned as a companion volume to the latter reference.

To quote from the preface, "It is hoped that the book may be of assistance to those who have to revise rapidly their knowledge of medicine in general or of some disease in particular, to the worried student whose final examinations are within sight and to the hurried practitioner from whose ken they have long passed, possibly even to the teacher with a lecture to prepare and to the examiner who, for the purposes of a *vive voce*, desires to renew for a brief period his knowledge of any of the essential details of medicine. The 'Synopsis' cannot replace a textbook to the student, and any attempt to make it do so will inevitably lead to failure."

Each disease is defined, and a short historical sketch is given, a general consideration as to etiology, mode of infection, bacteriology, morbid anatomy, symptomatology, types, complications and sequelae, diagnosis, prognosis and treatment, including prophylaxis, follows. By means of short summaries and special headings, the data that are of greatest importance have been clearly indicated. A full index has been provided.

THE PRINCIPLES AND PRACTICE OF MEDICINE DESIGNED FOR THE USE OF PRACTITIONERS AND STUDENTS OF MEDICINE Originally written by the late SIR WILLIAM OSLER, Bt, M.D., F.R.S. Eleventh edition Revised by THOMAS McCRAE, M.D., Professor of Medicine, Jefferson Medical College, Philadelphia Price, \$7.50 Pp 1,237 New York D Appleton & Company, 1930

The eleventh edition of Osler's "Principles and Practice of Medicine," as revised by Dr Thomas McCrae, hews to the line in presenting the fundamentals of medicine, principally adapted for the use of the medical student, but equally valuable for the general practitioner as a work of ready reference.

In revising the work, Dr McCrae has been confronted by the difficult task of deciding how much of the new has earned the right to displace the old in keeping the work up to date and yet compressed into the confines of a not too bulky single volume. Traditionally, a definite and apparently successful effort has been made to retain everything that was characteristic of Osler. This text was one of the great interests of Osler's life, and the present edition has lost none of the original Osler flavor, this is its chief charm. Although much new material has been added, a proper perspective in describing the average picture of disease processes is preserved. Uniformity of style and clarity of expression particularly recommend the book for the use of the student. In all particulars, Osler's book remains the standard text, a position it has occupied for the past thirty-eight years.

A SYSTEM OF CLINICAL MEDICINE DEALING WITH THE DIAGNOSIS, PROGNOSIS, AND TREATMENT OF DISEASES FOR STUDENTS AND PRACTITIONERS By DR THOMAS D SAVILL Eighth edition Price, \$10 Pp 1,017, with 167 illustrations New York William Wood & Company, 1930

This edition has been completely revised under the supervision of Agnes Savill. Many of the chapters have been rewritten by Dr Savill or by other English physicians, and an effort has been made to bring the material up to date.

The book is fairly comprehensive and covers in a brief way most matters of medical interest. The diseases are discussed from the standpoint of symptoms, the etiology, course of the disease, prognosis and treatment are dealt with later. On the whole, the descriptions of diseases are accurate and clearly written. Treatment seems to be a weak point throughout the book. Many drugs that have long been known to be of doubtful, if any, value are mentioned as being efficacious. There seems to be no critical discussion of therapy, and the advice is often misleading.

DER OPERIERTE MAGEN By PROF DR HERMANN MEYER-BURGDORFF and DR WALTER SCHMIDT, Göttingen Paper Price, 9.60 marks Pp 114, with 146 illustrations Leipzig Georg Thieme, 1930

The literature on gastro-enterology heretofore has lacked an adequate presentation of the subject of postoperative gastric disturbances. In this monograph the authors describe their investigation of these disturbances in about 400 patients whose stomachs had been subjected to various operative procedures. The methods employed were those of careful clinical study and detailed roentgenologic examinations, the technic now in vogue on the Continent being used. This phase of the work has been done exceedingly well, for the task of obtaining definite roentgenologic information in a case in which an operation has been performed on the stomach is admittedly difficult. The numerous illustrations are excellent.

The various procedures of gastric surgical intervention are described in turn, sufficient consideration being given to the technic, the disturbances that may result and their clinical manifestations and the changes in the form of the stomach, in its secretion and in its motor function. Recurrent gastric carcinoma and recurrent peptic ulceration are discussed in detail. The bibliography is splendid.

The work will interest all students of gastric disease, internists, surgeons and roentgenologists.

THE RELATION OF ACHLORHYDRIA TO PERNICIOUS ANEMIA *

ELI MOSCHCOWITZ, M D

NEW YORK

Achlorhydria is the most constant symptom of pernicious anemia. Indeed, the reported cases of pernicious anemia in which hydrochloric acid was present are so few that doubt has been raised as to their validity. In my experience I do not recall an instance in which achlorhydria was absent. Cases in which hydrochloric acid was present eventually proved to be diseases other than pernicious anemia. Therefore, achlorhydria may be regarded as the most decisive differential sign in establishing the diagnosis of pernicious anemia.

Following Hunter, until recently achlorhydria was regarded as secondary and consequent to gastro-intestinal sepsis of unknown origin. With more intensive study, it becomes evident that this view is untenable for the following reasons: 1. If achlorhydria were secondary, one should expect occasionally in the course of the development of anemia to witness the gradual diminution of hydrochloric acid from normal to subacidity and finally to achlorhydria. But such a diminution has not been noted. At the first examination, achlorhydria is invariably present. 2. The acid never appears, no matter how long the remission. Martius first conceived that achlorhydria was primary and represented an element in the predisposing constitution of pernicious anemia. A host of additional observations made in the past decade indicate strongly that this conception is correct. 3. Achlorhydria precedes the development of pernicious anemia. Hurst¹ found achlorhydria long before the onset of the clinical evidences of pernicious anemia, once, twelve years previously. Since then numerous similar instances have been reported, such as the case of Faber² (ten years) and Sturtevant³ (fourteen years). Riley⁴ reported many such cases in which the duration was

* Submitted for publication, Nov. 26, 1930.

1 Hurst, Arthur F., and Stewart, Mathew J. *Gastric and Duodenal Ulcer*, New York, Oxford University Press, 1929.

2 Faber, K., and Gram, H. C. *The Association of Achylia and Anemia of Different Types in Three Members of the Same Family*, *Arch. Int. Med.* **34**: 827 (Dec.) 1924.

3 Sturtevant, M. *Achlorhydria Preceding Pernicious Anemia*, *J. A. M. A.* **85**: 1638 (Nov. 21) 1925.

4 Riley, W. H. *Achlorhydria Preceding Pernicious Anemia*, *J. A. M. A.* **85**: 1908 (Dec. 12) 1925.

from four to twenty-five years Connor⁵ referred to additional observations and reported three cases in which achlorhydria preceded pernicious anemia from two to eighteen years. This observation explains the frequency with which one obtains the history of diarrhea (gastrogenous) preceding the onset of pernicious anemia. Since achlorhydria often precedes pernicious anemia by a number of decades, the question arises whether achlorhydria and the consequent anemia are congenital and transmissible, and therefore familial characteristics.

A discussion of the entire relation of achlorhydria to these hereditary characters leaves much to be desired, for the gaps in the knowledge of the subject are huge. Even the discovery of the existence of achlorhydria is not as simple as it appeared to be when the Ewald meal was the standard test. The fractional test meal has considerably reduced the number of true cases of achlorhydria, furthermore, this residuum has again been shrunken by the discovery that with the neutral red reaction and histamine, hydrochloric acid may be demonstrated when it was previously absent. All previous statistics as to the percentage incidence of achlorhydria in various maladies and under normal conditions therefore require complete revision.

FAMILIAL INCIDENCE OF ACHLORHYDRIA AND OF PERNICIOUS ANEMIA

No statistics are available that are based on modern methods of examination. The older statistics based on the Ewald meal are obviously too high. In 1921, Bennet and Ryle⁶ found an incidence of 4 per cent with the fractional method. In 1924, Baird, Campbell and Hern⁷ reported an incidence of 3.5 per cent with the same method. I do not know what the percentage of incidence would be with neutral red or histamine. Furthermore, as Connor⁵ and others have shown that the percentage of achlorhydria increases in each decade, a "normal" figure for all ages offers only indifferent information. Therefore, sound statistics on the normal incidence of achlorhydria are much desired. I am told by Dr. Asher Winkelstein, chief of the gastro-intestinal clinic at Mount Sinai Hospital, New York, that in his clinic when repeated and varied fractional test meals are used and a reaction to combined neutral red and histamine is elicited, the incidence of achlorhydria is 0.21 per cent. He supplied me with the following statistical data compiled in the achylia gastrica statistics in the gastro-intestinal clinic of Mount Sinai Hospital. 1. All of these cases were true achlorhydria as proved

5 Connor, H. M. Hereditary Aspect of Achlorhydria in Pernicious Anemia, *J. A. M. A.* **94** 606 (March 1) 1930.

6 Bennet, T. I., and Ryle, J. A. *Guy's Hosp. Rep.* **71** 268, 1921.

7 Baird, M. McC., Campbell, J. H. M., and Hern, J. R. *Guy's Hosp. Rep.* **74** 339, 1924.

by repeated test meals and tests with neutral red and histamine 2 The symptoms were vague—diarrhea, constipation, abdominal pains, anemia, and possible disease of the gallbladder 3 Proved cases of pernicious anemia, subtotal gastrectomy, carcinoma, etc., were not included In 2,348 consecutive patients, 49 cases occurred, making the incidence 0.21 per cent, there were 25 males and 24 females

The age incidence was as follows from 20 to 30 years of age, 6 cases, from 30 to 40, 9 cases, from 40 to 50, 20 cases, from 50 to 60 4 cases, and from 60 to 70, 8 cases

There is no doubt that achlorhydria with or without pernicious anemia is frequently familial In 20 or 30 cases of pernicious anemia, Martinez⁸ found achlorhydria in both parents and in 2 or 3 members of the family In another family, the great grandmother, the grandmother, 4 grandchildren and 5 of the 13 greatgrandchildren had achlorhydria In a small series of cases studied with Dr Crohn some years ago, it was found that about 40 per cent of the apparently normal children of patients with pernicious anemia had achlorhydria Hurst⁹ reported a number of cases of achlorhydria in the relatives of patients who had pernicious anemia or combined sclerosis Dorst¹⁰ reported a family in which 5 members had pernicious anemia, while 4 of the remaining apparently normal members showed achlorhydria Weinberg¹¹ examined 22 children and 2 sisters of 12 patients with pernicious anemia, 9 of the children and a sister showed achlorhydria In another family, 3 of the 4 children, aged 6, 10 and 14, showed achlorhydria Mustelin¹² reported a family in which a case of pernicious anemia occurred in each of three generations A fair proportion of other members of the family revealed achlorhydria, some of whom presented an anemia of the chlorotic type Mustelin regarded achlorhydria as a dominant hereditary character

The entire subject has recently been studied by Connor, who used the extensive resources of the Mayo Clinic With the fractional test meal alone he found an incidence of 14.2 per cent of the cases of achlorhydria in a series of 5,000 patients suffering from various diseases exclusive of pernicious anemia Of 154 blood relatives of persons with pernicious anemia, the gross percentage of those with achlorhydria was 25.9 per cent Connor expressed the belief that more than half of these blood relatives were healthy, so that the high incidence of achlorhydria is significant Of especial significance, brought out by Connor's studies, is the fact that the proportion of achlorhydria in these

8 Martinez, P. N. *Med iberica* **1** 118, 1927

9 Hurst, A. F. *Lancet* **1** 111, 1923

10 Dorst, S. E. *Am J M Sc* **172** 173, 1926

11 Weinberg, F. *Ztschr f ang Anat* **6** 289, 1920

12 Mustelin, O. *Acta med Scandinav* **56** 411, 1922

blood relatives rises with each decade, except in the sixth (see table)

What the drop in the seventh decade signifies was not apparent to Connor. He concluded

From these figures it seems to be strongly indicated that, when correction is made for age and sex, achlorhydria has a distinct tendency to occur more frequently among blood relatives of patients who have pernicious anemia than among normal persons or among persons who have a great variety of other diseases. This may mean that there is an inherited tendency to the occurrence of achlorhydria in many blood relatives of patients with pernicious anemia over and above any such tendency among patients having various other diseases, and even among those having gastro-intestinal symptoms. It seems unlikely, however, that the achlorhydria itself is inherited, but that the tendency to its development later may be an inherited factor.

Achlorhydria According to Age Groups Among Blood Relatives of Patients with Pernicious Anemia (Connor)

Age in Decades	Relatives	Subjects with Free Hydrochloric Acid	Subjects with Achlorhydria	Proportion with Achlorhydria, per Cent
10 to 19	13	12	1	7.6
20 to 29	37	32	5	13.5
30 to 39	45	36	9	20.0
40 to 49	26	14	12	46.1
50 to 59	17	12	5	29.4
60 to 69	14	6	8	57.1
70 to 79	2	2		
Total	154	114	40	25.9

The observations of Connor are significant, even if, as seems likely, the absolute values will be somewhat less when more precise methods of determining achlorhydria are employed. Their greatest significance lies in the light that they throw on the constitutional element in pernicious anemia. This will be more fully evident after the discussion of the heredity aspects of pernicious anemia.

THE HEREDITY OF PERNICIOUS ANEMIA

There is no doubt that pernicious anemia is not a congenital disease. Pernicious anemia is practically unknown in the first decade and extremely rare in the second. Naegeli¹³ reported cases of pernicious anemia in 3 children, aged 8, 11 and 12 years. He expressed the belief that the case of Escherich, who reported pernicious anemia in a child of 4, is not valid because the blood criteria were not sufficiently precise. In the carefully studied series of cases reported by Willson and Evans¹⁴ the youngest patient was between 10 and 20 years

¹³ Naegeli, O. *Blutkrankheiten und Blutdiagnostik, Lehrbuch der morphologischen Hamatologie*, Leipzig, Veit & Company, 1923.

¹⁴ Willson, C. R., and Evans, F. A. *Bull. Johns Hopkins Hosp.* **35**: 38, 1924.

of age In 111 cases, none occurred between the ages of 1 and 10, 0.9 per cent of the cases occurred between 10 and 20, 2.7 per cent, between 20 and 30, 2.3 per cent, between 40 and 50, and 3.3 per cent, between 50 and 60 The decline of the rate of pernicious anemia in people past 60 years of age is probably due to the fact, as Meulengracht¹⁵ said, that most patients die of anemia before they reach this age The familial character of pernicious anemia has been clearly established I have seen a number of such cases, while numerous instances were reported by Barker,¹⁶ Gram,¹⁷ Faber and Giam,² Patek,¹⁸ Grinker,¹⁹ Dorst,¹⁰ Meulengracht,²⁰ Hurst,¹ Weinberg,¹¹ Tscherning,²¹ Gulland and Goodall²² Tichter²³ found a history of heredity in 4.2 per cent of 140 patients with pernicious anemia admitted to the Eppendorf Krankenhaus In a series of 90 patients, Carey²⁴ found that 10 gave a history of probable pernicious anemia in the family A patient told me that pernicious anemia was diagnosed in 5 members of her family in three generations Levine and Ladd²⁵ found that pernicious anemia was familial in 6 per cent of their cases Studies on the hereditary nature of pernicious anemia are still incomplete, because the precise diagnosis of pernicious anemia has been developed comparatively recently, and it will require observations on three and more generations before it can be determined (1) whether pernicious anemia is always hereditary or whether it is a biologic sport, (2) whether it follows the mendelian law, and (3) whether it is a dominant or a recessive character Numerous instances have been reported in which pernicious anemia occurred in parent and child, but Mustelin's case is apparently the only instance of pernicious anemia in three generations, a grandmother aged 69, a daughter aged 44, and a granddaughter aged 25 The difficulty in determining accurately the hereditary incidence is due to the fact that it will never be known whether pernicious anemia might not have developed in those who have died in early life Bringing these facts con-

15 Meulengracht, C *Am J M Sc* **169** 177, 1925

16 Barker, L F *The Etiology and Treatment of Pernicious Anemia*, J A M A **87** 80 (July 10) 1926

17 Gram, H C *Ugesk f læger* **91** 1135, 1929

18 Patek, A J *Family Pernicious Anemia*, J A M A **56** 1315 (May 6) 1911

19 Grinker, Roy R *Pernicious Anemia, Achylia Gastrica and Combined Cord Degeneration and Their Relationship*, Arch Int Med **38** 292 (Sept) 1926

20 Meulengracht, C R *Folia haemat* **32** 300, 1926

21 Tscherning, R *Deutsche med Wchnschr* **52** 707, 1926

22 Gulland, G L, and Goodall, A *The Blood*, ed 3, Edinburgh, W Green & Son, 1925

23 Tichter *Inaugural Thesis*, Berlin, 1927

24 Carey, J B *Minnesota Med* **9** 385, 1926

25 Levine, S A, and Ladd, W S *Bull Johns Hopkins Hosp* **32** 254, 1921

cerning the hereditary and familial incidence of pernicious anemia in accord with the corresponding incidence of achlorhydria, one may infer that there is a strong constitutional element in pernicious anemia in the sense that there is a transmissible background for the disease and that an important feature in this element is the tendency to acquire achlorhydria. Curiously, this element differs from other constitutional characteristics in that achlorhydria itself is not transmissible. Comprehensive statistics on the gastric contents of newly born infants are lacking, but pediatricians testify that achlorhydria in infants is extremely rare. Even in early childhood achlorhydria is probably extremely rare. Copeman and Hill²⁶ reported 7 cases of achlorhydria in 66 normal children between the ages of from 12 to 15. Katsch²⁷ collected only a few cases. One was that of a child, aged 12. He quoted Schmidt,²⁸ who claimed to have seen achlorhydria in association with various degenerative stigmas, and Albu²⁹ who reported a number of cases occurring in patients below the age of 7.

THE RELATION OF ACHLORHYDRIA TO BOTHRIOCEPHALUS LATENS ANEMIA

The hematologic and clinical picture of pernicious anemia and that of *Bothriocephalus* anemia are identical, even in respect to achlorhydria. The question arises: Is achlorhydria the result, or did it precede the infestation? One cannot definitely answer this question for the obvious reason that studies of the gastric contents of patients previous to the infestation with the worm are not available. But there is abundant circumstantial evidence that, as with cryptogenetic pernicious anemia, the so-called *Bothriocephalus* variety shows a strong familial tendency. It is well known that in certain countries, Finland for instance, where infestation with *Bothriocephalus* is extremely common, the incidence of pernicious anemia in these persons is small, being only 1 per cent according to Tallquist.³⁰ Now Schaumann,³¹ whose studies on *Bothriocephalus* anemia are the most comprehensive extant, found that in only 1 of 11 cases studied the gastric contents reacted to the phloroglucin-vanillin test. So far as I am aware, no mass studies on the gastric contents in *Bothriocephalus* anemia have been done since those of Schaumann, but judging from the scattered casuistic reports, achlorhydria has always

26 Copeman and Hill. *Lancet* **1** 718 (April 6) 1929.

27 Katsch, G. *Handbuch der inneren Medizin*, Berlin, Julius Springer, 1926, vol. 3, part 1.

28 Schmidt, quoted by Katsch (footnote 27).

29 Albu, quoted by Katsch (footnote 27).

30 Tallquist. *Ztschr f klin Med* **61** 427, 1907.

31 Schaumann. *Zur Kenntnis der sogenannten bothriocephalus Anämie*. Helsingfors, 1894.

been found. The case of Isaacs and Sturgis³² is particularly interesting because not only did achlorhydria persist for five months after expulsion of the worm, but the mother of the patient had true primary pernicious anemia. I have been informed of another case observed in Hamburg in which achlorhydria was noted both before and after the expulsion of the worm. Therefore, the probability is strong that achlorhydria is as constant an observation in *Bothriocephalus* as in primary pernicious anemia. Schaumann's original observations on *Bothriocephalus* anemia, published in a monograph in 1894, are exceedingly valuable as a clinical and diagnostic exposition. He did a remarkable piece of work. In 1910,³³ he published a paper in which he reported a follow-up of the cases of *Bothriocephalus* anemia that he had observed between 1883 and 1893, that is, from seventeen to twenty-seven years previously. This report is most illuminating, it reveals that the constitutional element is as manifest in *Bothriocephalus* anemia as in cryptogenetic pernicious anemia. Even in his original publication, Schaumann, with remarkable acumen, suspected that there must be a constitutional element in *Bothriocephalus* anemia, because he could not understand why anemia developed in such a small percentage of patients infested with *Bothriocephalus*. First Schaumann found that a considerable number of his patients (17 per cent) died, even after the worm was expelled. He also found that true primary pernicious anemia later developed in 7 of his patients with *Bothriocephalus* anemia who were "cured" after expelling the worm. Furthermore, he found that in 24 of the families, at least 2 of the members revealed clinical evidences of pernicious anemia, in 15 the anemia was associated with infestation with *Bothriocephalus*, in 7, it was cryptogenetic, and in 2 families it was both cryptogenetic and bothriocephalic. He also found, as others have since, that achlorhydria persisted after the expulsion of the worm. Based on his observations, in all of his publications, even up to his most recent one in 1925, Schaumann³⁴ expressed the belief that there is a constitutional background for the disease. In the light of modern conception it is intriguing to think that it is only those patients with achlorhydria who acquire pernicious anemia after infestation with *Bothriocephalus*. Unfortunately, there are a considerable number of facts that make one skeptical as to whether *Bothriocephalus* has anything to do with the development of the pernicious anemia. These facts are presented in the following paragraphs.

32 Isaacs, R., Sturgis, C. C., and Smith, M. Tapeworm Anemia. Therapeutic Observations, Arch Int Med **42** 313 (Sept) 1928.

33 Schaumann. Deutsche med Wchnschr **36** 1218, 1910.

34 Schaumann and Saltzman. Handbuch des Krankheiten des Blutes und blutbildenden Organe, Berlin, 1925, vol 2.

1 In certain areas of Finland where infestation with *Bothriocephalus* is extremely common, affecting from one quarter to one third of the population in certain districts, the number of patients in whom pernicious anemia develops is extremely small, less than 1 per cent according to Schaumann and Tallquist and at the most 0.5 per cent, according to Ehrstrom³⁵

2 If *Bothriocephalus* were an inciting agent of pernicious anemia, one should expect a much higher percentage of *Bothriocephalus* anemia as compared to the cryptogenetic variety in countries infested with *Bothriocephalus*. Even Schaumann and Saltzman's³¹ statistics show that of 44,087 patients admitted to the Helsingfors Hospital, the total percentage with *Bothriocephalus* anemia was 0.74 and, with cryptogenetic anemia, 0.44, a difference that is not impressive. Even this narrow difference may be partly accounted for by the fact that the diagnosis depended on the finding of the eggs of the worm in the stool. Cases have been reported by Neubecker³⁶ and Meyer³⁷ in which the worm was never found after repeated anthelmintic therapy, despite the constant presence of eggs in the feces.

3 The development of the anemia bears no relation to the number of parasites. Schaumann and Saltzman reported a number of instances in which as many as 78 or even 90 worms were expelled, although the patient at no time had anemia.

4 Schaumann and Saltzman also reported the cases of patients who have overcome a so-called *Bothriocephalus* anemia and who years later became reinfected without pernicious anemia developing.

5 These authors and Runeberg³⁸ reported the cases of several patients in whom anemia improved spontaneously even before the worm was expelled. Sturgis and Isaacs reported a case of *Bothriocephalus* anemia in which the patient recovered under liver therapy before the worm was expelled. Saltzman³⁹ reported typical reticulocytic reactions in *Bothriocephalus* pernicious anemia after liver therapy, with abrupt improvement in the blood picture agreeing with the results obtained by liver therapy in cryptogenetic anemia. He expressed the belief, nevertheless, that tapeworm anemia seems more often resistant to liver therapy than does cryptogenetic anemia. Further studies on an extensive scale of the effect of liver therapy in so-called *Bothriocephalus* anemia as compared to therapy by expelling the worm are desirable.

6 The extraordinary clinical similarity between cryptogenetic and *Bothriocephalus* pernicious anemia, the fact that true pernicious anemia

35 Ehrstrom, R. Ztschr. f. klin. Med. **105** 106, 1927

36 Neubecker. Inaugural Thesis, Königsberg, 1898

37 Meyer. Med. News **86** 633, 1905

38 Runeberg. Deutsches Arch. f. klin. Med. **41** 304, 1887

39 Saltzman, F. Nederl. tijdschr. v. geneesk. **73** 4463, 1929

is associated so commonly with *Bothriocephalus* anemia in families in which the latter is present, and that in Schaumann's collection of 14 "cured" cases of *Bothriocephalus* anemia the cryptogenetic variety developed in later years are circumstances that make one suspect that the two diseases are identical. Curiously, even the incidence of *Bothriocephalus* anemia according to decades corresponds precisely to that of the cryptogenetic variety (Schaumann). There are certain negative evidences.

7 *Bothriocephalus* is not the only parasite that has been brought into causal relationship with pernicious anemia, a host of other helminths have been reported as the "causes" of pernicious anemia, and curiously the number of such cases reported is proportionate to the frequency with which the parasite is encountered in man. Thus in the order of frequency, cases of pernicious anemia have been reported due to *Taenia saginata*, *Ascaris*, *Taenia solium*, *Trichocephalus dispar*, *Ancylostoma*, *Hymenolepis*, *Anguillula intestinalis*, *Lambia intestinalis* and *Distoma hepaticum*. Wiemer and Derra⁴⁰ reported that 79 per cent of their patients with pernicious anemia gave a previous history of having had worms (mostly *Taenia* and *Ascaris*), and that the course of the disease was not influenced in the least in those in whom the worm was expelled. It is difficult to believe that the presence of these worms in patients with the blood picture of pernicious anemia represents more than the mere association, according to the law of chance, of two separate and unrelated conditions. Such associations are exceedingly common in medical practice, and often require considerable circumspection. It is now understandable why the helminthic origin of certain cases of pernicious anemia was first propounded in Finland. Outside of this country, the total number of reported cases is exceedingly small, according to Ehrstiom only 29, and practically all of these cases were imported.

Only one piece of evidence lends support to the belief that *Bothriocephalus* causes pernicious anemia, and that is the frequency with which cures are reported after expulsion of the worm. Schaumann claimed that in about 17 per cent of such cases failures occurred, others reported less, but apparently their testimony comes from insufficient observation and from a desire to make the etiologic relationship complete. From a rather careful perusal of the reported cases, I gather that the percentage of failures is larger than this optimism warrants. In most reported "cures" the subsequent history is not stated. With a disease of such a long life cycle as pernicious anemia, it is always possible that the disease passed into a stage of remission, an event that before liver therapy was more often spontaneous than otherwise, and that a proper "follow up" would reveal a much higher percentage of failures. Certainly the considerable number of "cured" cases of *Bothriocephalus*

40 Wiemer, P., and Derra, E. Med Klin 24 168, 1928

anemias in which the cryptogenetic variety ultimately develops adds support to this view

When all these facts are taken into consideration, it is apparent that a resurvey of the entire field of *Bothriocephalus* anemia is necessary. So far as the facts allow, one may justifiably say that it is not proved that *Bothriocephalus* is the origin of pernicious anemia. Elstrom denied such an origin entirely.

Tallquist's⁴¹ experiment in which a lipoid substance derived from the proglottis of the *Bothriocephalus* worm caused a hemolytic anemia has not been confirmed by Hirschfeld,⁴² Schminke⁴³ or Flury⁴⁴

THE RELATION OF ACHLORHYDRIA TO OTHER ANEMIAS

Relation to Secondary or Chlorotic Types of Anemia—Clinically, one is struck by the frequency of anemia of the secondary or chlorotic types in patients with achlorhydria. In a series of 207 cases of achlorhydria, Faber found pernicious anemia in 22. In 52 cases there was simple chlorotic anemia which he found extremely resistant to treatment. He did not believe that chlorotic anemia changed into pernicious anemia, but as it probably takes a considerable time for pernicious anemia to develop after achlorhydria has set in this statement must not be taken too seriously. Weinberg⁴⁵ reported the observations on the blood in 77 patients with achlorhydria. In 14 per cent, the hemoglobin was below 80 per cent, in 35 per cent, the red cell count was below 4,500,000. In 38 per cent, the color index was over 1, and in 60 per cent, the leukocytes were low. He frequently found normoblasts, myelocytes, myeloblasts and poikilocytes in patients in whom the hemoglobin was normal. He regarded these observations as representing the early phase of pernicious anemia. Mustelin reported achlorhydric members of families with pernicious anemia of the chlorotic type. Meulengracht described the case of a child with achlorhydria, a blood relative in a family in which pernicious anemia was present, examination showed hemoglobin, 98 per cent, red cells, 3,000,000, color index, 1.25, megalocytosis, average red cell diameter, 8.8 mm, leukopenia, bilirubinemia, urobilinuria, and glossitis. In 50 per cent of 134 patients with achlorhydria, Borgbjoerg and Lottrop⁴⁶ found that there was an anemia usually of the simple type and mild. In 22 the color index was over 1. Megalocytosis was found in 15 per cent, most often in patients

41 Tallquist. Ztschr f klin Med **61** 427, 1907

42 Hirschfeld, quoted by Schaumann and Saltzman (footnote 34)

43 Schminke, W., and Flury, F. Arch f exper Path u Pharmakol **64** 126, 1910-1911

44 Flury, F. Arch f exper Path u Pharmakol **67** 275, 1911-1912

45 Weinberg, F. Deutsches Arch f klin Med **126** 447, 1918

46 Borgbjoerg, A., and Lottrop, M. C. Hospitalstid **72** 745, 1929

with a high hemoglobin value. They expressed the belief that a careful examination of the blood, especially in cases with a high percentage of hemoglobin, would probably reveal some cases of pernicious anemia in the early stage. Carey investigated 23 cases of achlorhydria. Three showed color indexes of over 1. The blood smears of those with a high index showed macrocytes and polychromasia. He also reported 4 cases in which achlorhydria and anemia had been demonstrated for various intervals of years before pernicious anemia developed. One case in which blood counts are tabulated had shown a high index, although anemia was hardly apparent. Kohn⁴⁷ examined the blood of 10 patients with achlorhydria proved by testing with neutral red. He found a high color index in 9. In a few cases there were myelocytes and in 1 a normoblast. I have observed a patient who for some months previous to the development of the typical hematologic picture of pernicious anemia showed an unexplainable secondary anemia.

The entire question centers around the following problems:

1. Does pernicious anemia eventually develop in all patients with true achlorhydria? As the majority of cases of pernicious anemia occur in the fourth and fifth decades, it will take an accurate study of a family with pernicious anemia covering three generations before this question can be answered.
2. What is the earliest blood picture in patients in whom pernicious anemia develops? Obviously, by the time the patient feels badly enough to present himself to the clinic, the disease may be considered already well advanced. If the few observations previously mentioned may be accepted, one gathers that the changes in the blood are already profound and various in what may be called the preclinical stage. But it is apparent that much further study is required to gain a proper perspective, not so much by casual examination, but more especially by studying the development of the changes in the blood from the earliest phases to the mature picture. Nothing is known, for instance, as to when megalocytosis, probably the more constant feature of the examination of the blood in pernicious anemia, arises in the preclinical stage.

Relation of Artificial Achlorhydria to Anemia—The occasional reports of the hematologic pictures of pernicious anemia following artificial achlorhydria produced by complete resection of the stomach have suggested that achlorhydria bears some causal relation to anemia. Such reports are remarkably few, and a number of these will not pass criticism. In Moynihan's⁴⁸ patient, "severe anemia" developed three years after the resection for cancer. He had one remission, but died within a year. Autopsy revealed only an intense anemia and no recur-

47 Kohn, E. *Wien klin Wchnschr* **41** 1221, 1928.

48 Moynihan, B. *Lancet* **2** 430, 1911.

ence Hartmann⁴⁹ reported a well observed case of complete gastric resection for carcinoma. Achlorhydria was present before the operation. Two years later, the patient showed the hematologic evidences of pernicious anemia. Dennig⁵⁰ reported the case of a man, aged 41, in whom the typical blood picture of pernicious anemia with symptoms of the cord developed eight years after complete gastric resection for ulcer. He was "cured" by liver therapy, but died one year later from gangrene of the lung. Hochrein⁵¹ reported 2 cases of resection of the stomach for cancer and ulcer respectively. In the first patient the blood picture resembled pernicious anemia, in the second, a secondary anemia. Both cases responded to liver therapy. In Scheidel's⁵² patient, pernicious anemia developed six years after a high and incomplete gastric resection. Liver therapy was successful. Morawitz⁵³ reported 3 cases of anemia following gastric resection. One showed the hematologic evidences of pernicious anemia, the second, secondary anemia, and the third, anemia of the aplastic variety. All of the patients responded well to liver therapy. Hurst spoke of 5 cases within his knowledge, 4 occurred following partial gastrectomy, and 1, after gastrojejunostomy. Castle⁵⁴ referred to 9 cases collected by Finney and Rienhoff,⁵⁵ in which complete gastrectomy was performed, the patients surviving for at least a year, in 2 (Hartmann and Dennig's cases) pernicious anemia apparently developed. The evidence favoring the development of pernicious anemia after complete gastrectomy is by no means complete. There is no reason why a common disease like pernicious anemia should not be associated with maladies so common as gastric carcinoma or ulcer. Furthermore, gastric cancer and ulcer are not infrequently treated by complete or nearly complete resection, so that the probability is likely, according to the law of chance, that pernicious anemia might occasionally seem to follow such an operation. Of course, it is essential for purposes of observation that the resection be complete in order to be sure that achlorhydria is complete. In 2 of 9 such cases quoted by Castle from Finney and Rienhoff's statistics (those of Hartmann and Moynihan), pernicious anemia developed, a percentage that is not very impressive, even granting that Moynihan's case is a valid one of pernicious anemia, which is doubtful. Of course, it is possible that after gastric resection a more

49 Hartmann, H. R. *Am J M Sc* **162** 20, 1921

50 Dennig, H. *Munchen med Wchnschr* **76** 633, 1929

51 Hochrein, M. *Munchen med Wchnschr* **76** 1327, 1929

52 Scheidel, H. *Med Klin* **26** 247, 1930

53 Morawitz, P. *Med Klin* **26** 261, 1930

54 Castle, W. B., quoted by Sturgis, C. C., and Isaac, R. *Desiccated Stomach in the Treatment of Pernicious Anemia*, *J A M A* **93** 747 (Sept 7) 1929

55 Finney and Rienhoff, quoted by Castle, W. B. *Brit M J* **1** 1120, 1929

prolonged period of observation would reveal a higher percentage developing pernicious anemia. More suggestive is the case of Du Bois reported by Castle in which a blood picture of pernicious anemia with achlorhydria developed in a girl aged 13, an age most unusual for the appearance of this disease. Although she responded to liver therapy, other symptoms necessitated an operation, when a tight stenosis of the pylorus due to enlarged tuberculous glands was found. Castle expressed the belief that achlorhydria may have been due to stenosis and that pernicious anemia was the result. It would be interesting to follow this patient to determine whether she eventually maintained the clinical evidences of pernicious anemia. Altogether one cannot make a very convincing argument concerning the development of pernicious anemia from an artificial achlorhydria obtained by complete resection, even though such a contention seems reasonable. To settle this problem, better and more extensive observations are necessary.

Relation of Achlorhydria to the Severe Anemia of Pregnancy—It is impossible to discuss this relationship with even any attempt at precision because the gaps in the reported observations are large. The not uncommon secondary and chlorotic types of anemia are not of interest in this paper, I shall deal with only the anemias that resemble the pernicious type. Apparently these cases can be divided into those in which achlorhydria is present and those in which it is not. Such anemias may arise in any month of pregnancy and even after parturition. Anemia may arise after the first pregnancy, indeed, Schaumann and Saltzman⁵⁴ hold that it is more common in primipara than in multipara. It may recur after each pregnancy, but Esch,⁵⁶ Gurowitch⁵⁷ and Naegeli⁵⁸ reported cases in which a subsequent pregnancy or pregnancies were not followed by anemia. The early cessation of pregnancy apparently has no effect on anemia. McSwiney⁵⁸ and Balfour, Wills and Mehta⁵⁹ described a form of anemia that is common in India occurring more frequently in pregnant than in nonpregnant women. The color index is high, the blood smear shows a few nucleated red cells, mostly normoblasts, free hydrochloric acid is present, and there are no neurologic or lingual signs. It is the consensus that the severe anemias of pregnancy respond admirably to treatment with liver.

There can hardly be any question that some of the reported cases of pernicious anemia following pregnancy represent chance associations of two rather common conditions. I saw such a case several years ago. The clinical picture of pernicious anemia was perfect, even as to glos-

⁵⁶ Esch, P. *Zentralbl f Gynak* **50** 857, 1926.

⁵⁷ Gurowitch. *Inaugural Thesis*, Zurich, 1912.

⁵⁸ McSwiney, S. A. *Indian M Gaz* **62** 487, 1927.

⁵⁹ Balfour, M. I., Wills, L., and Mehta, M. M. *Indian J M Research* **17** 777, 1930.

sitis and achlorhydria, and the patient responded nicely to treatment with liver. Of course, it is possible that pregnancy is the inciting factor in patients who have achlorhydria. A complete study and follow-up are necessary before a differentiation can be made between cases of true Addisonian anemia and those that are not.

Relation of Achlorhydria to the Anemia of Sprue—Here again knowledge is deficient. It is well known that not only secondary anemia but a clinical picture closely resembling that of pernicious anemia is often associated with sprue, that is, these patients show the typical hematologic picture, achlorhydria and glossitis. According to Wood,⁶⁰ changes of the cord occur often in sprue, but less frequently than in the cryptogenetic variety. It is difficult to obtain an estimate in mass figures of the frequency in which achlorhydria occurs in sprue, not only because the determinations were made before modern methods were devised, but because there are no available statistics. Wood said that it occurs "more often than one would infer", that it occurs in the late phases of the disease, and that free hydrochloric acid is present in the early stages. In 6 of 13 cases Bovaird⁶¹ found an acidity, in 1 patient subacidity was noted and 6 were normal. Newham, Morris and Manson-Bahr⁶² reported achlorhydria in 2 of 5 observed cases of sprue. I am informed that in Porto Rico the percentage of achlorhydria in sprue is about 25 per cent. Hegler's⁶³ report is interesting, because his patient in whom a clearcut picture of pernicious anemia with achlorhydria developed had had hyperchlorhydria two years earlier. An investigation by the Bombay Commission⁶⁴ revealed that about one half of the patients examined had achlorhydria.

In order to determine the relation of achlorhydria to the anemia of sprue, one would have to know certain other data. For instance, does achlorhydria develop in sprue or is it a precursor of the disease? Does anemia occur in sprue only in the cases in which achlorhydria is present? In true cases in which recovery occurs does the achlorhydria return? Why is it that liver therapy as a rule is unsuccessful in the treatment for the anemia of sprue? Probably the reason is that the anemia of sprue and of pernicious anemia are entirely separate diseases and that one does not pass into the other and vice versa, no matter how close the clinical resemblance may be. At all events, these are the problems that must be left for future study.

60 Wood, E. J. *Am J M Sc* **169** 28 1925

61 Bovaird, D. A Study of Tropical Sprue, or Psilosis. *J A M A* **77** 753 (Sept 3) 1921

62 Newham, H. B., Morris, R. M., and Manson-Bahr, P. H. *Lancet* **2** 269, 1926

63 Hegler, C. *Deutsche med Wchnschr* **54** 1505, 1928

64 Report of Bombay Bacteriological Laboratory for the Year 1924, Bombay, 1925

MECHANISM OF ACHLORHYDRIA ON ERYTHROPOIESIS

The data in the preceding review suggested strongly that the altered gastric secretions of patients with pernicious anemia has some profound effect on erythropoiesis. That achlorhydria alone is not responsible is evident because hydrochloric acid is useless in the treatment for pernicious anemia. It is futile to review the various theories whereby a gastro-intestinal sepsis was supposed to be induced by the absence of hydrochloric acid thus producing the anemia, because since the fundamental work of Castle and Sturgis and Isaacs⁶⁵ these theories may be discarded. Castle showed that the incubation of normal gastric juice on beef muscle produced a substance that brought about a remission in patients with pernicious anemia precisely comparable to that produced by liver therapy. By well controlled experiments, he showed that neither the hydrochloric acid alone nor the beef muscle alone, or both administered separately had any effect on the disease. It seems that this proof establishes the fact that the achlorhydria alone is not the cause for the absence of erythropoiesis, but that it represents the dominant indication of the specifically altered gastric secretion in pernicious anemia. Castle's work suggested that some unknown substance in normal gastric secretion might be the erythropoietic factor, whereupon Sturgis and Isaacs⁶⁵ prepared a dry extract from the normal stomach of a hog which, when given to patients with pernicious anemia, produced a characteristic response in the reticulocytes and a remission comparable to that obtained by liver therapy.

It would be hazardous at present to venture any theory as to the cause of pernicious anemia. The work that has been done in the past few years in America is portent with many possibilities. All that one can say at present is that pernicious anemia is partly the result of a deficiency and partly of a defective gastric hormone, of which achlorhydria is the most tangible symptom.

SUMMARY AND CONCLUSIONS

1 Achlorhydria is such a constant sign in pernicious anemia that probably no case is valid unless achlorhydria is present.

2 Achlorhydria is not the result of the disease but is primary. Evidence for this is shown in the fact that there is no diminution of hydrochloric acid in the progress of a case of pernicious anemia and that achlorhydria is present from the onset, that achlorhydria persists in the stage of remission and that it has been found frequently for years before pernicious anemia became manifest.

⁶⁵ Sturgis, C. C., and Isaacs, R. Desiccated Stomach in the Treatment of Pernicious Anemia, *J. A. M. A.* 93:747 (Sept. 7) 1929.

3 Achlorhydria occurs normally in a small percentage of persons. In order to determine this percentage, it is essential that mass studies be made with not only the fractional method of testing gastric secretion, but the tests with neutral red and histamine as well. The percentage of persons with achlorhydria apparently increases with each decade. It is extremely rare in childhood.

4 Achlorhydria is often present in certain families. In families in which a case of pernicious anemia has occurred, the incidence of achlorhydria is much higher than normal. As this incidence increases in each decade and as achlorhydria is exceptional in childhood, achlorhydria itself is not transmitted but only the tendency thereto.

5 Pernicious anemia is frequently hereditary and familial. Whether pernicious anemia is always hereditary and whether it is a dominant or recessive character and transmissible according to the mendelian law cannot be determined until such families are studied with particular reference to achlorhydria and with accurate hematologic examinations being made for three generations at least.

6 The available evidence is not convincing that *Bothriocephalus latus* causes pernicious anemia. There is ground for believing that such reported cases represent instances of true pernicious anemia that happen to be associated with infestation with *Bothriocephalus*.

7 There is a definite relation between achlorhydria and anemia, of the pernicious, secondary and chlorotic types. The blood of relatives of patients with pernicious anemia shows changes, which sometimes may be regarded as the earliest or preclinical evidence of the disease. For diagnostic purposes, it is important to recognize this preclinical phase.

8 The development of pernicious anemia after an acquired achlorhydria, for instance after complete gastric resection, has not definitely been proved.

9 Many of the so-called "severe anemias" of pregnancy (exclusive of those due to hemorrhage or sepsis) represent cases of true pernicious anemia in which the patients have become pregnant. Whether the pregnancy is the inciting factor in patients with a constitutional tendency remains to be proved.

10 The anemia of sprue is often associated with achlorhydria. It is not yet established how often achlorhydria is acquired or is a constitutional tendency in this disease.

11 Achlorhydria is the most tangible but not the only evidence of the constitutional background of pernicious anemia. In all probability pernicious anemia represents a combination of a deficiency disease and a lack of a gastric hormone.

CIRCULATION IN ARTERIOVENOUS ANEURYSM

BEFORE AND AFTER OPERATION ¹

CARTER SMITH, M D

ATLANTA, GA

An arteriovenous fistula in the human being offers an excellent opportunity to study the mechanics of the circulation under normal and abnormal conditions in the same person. It is one of the few diseases of the cardiovascular system that can be altered completely and permanently by an operative procedure. A physiologic study of the circulation in patients with an arteriovenous fistula is of interest, not only because of the phenomenal changes that sometimes occur, but because it affords an opportunity for a more complete understanding of other diseases of the cardiovascular mechanism.

These observations were undertaken in an attempt to determine the physiologic effect produced on the circulation by a large fistulous communication of six years' duration between the deep femoral artery and vein. The circulation was studied before and after obliteration of the fistula by operation. The secondary effects of this long-standing communication were quite marked, the heart was greatly enlarged, there was considerable sclerosis of the small vessels, and there had been two periods of congestive heart failure.

REVIEW OF THE LITERATURE

During the past ten years, much experimental work has been done in an effort to explain the abnormal physiology of this condition. Detailed studies of the circulation in the dog have been made before and after experimental production of an arteriovenous fistula. Harrison, Dock and Holman¹ found that the cardiac output of the dog was approximately doubled following the production of an arteriovenous fistula, and that closure of the fistula resulted in a 48 per cent decrease in the circulatory minute volume. They believed that the cardiac hypertrophy associated with arteriovenous aneurysms was due to an actual increase in the amount of work done by the heart and to an

² Submitted for publication, Oct 31, 1930

^{*} From the Medical and Surgical Clinics of the Emory University Division of the Grady Hospital

¹ Harrison, T R, Dock, W, and Holman, Emile. Experimental Studies in Arteriovenous Fistulae. Cardiac Output, Heart **11** 337, 1924

increase in the total volume of blood Holman² showed that the formation of an arteriovenous fistula is followed by an acceleration of the heart rate and a fall in blood pressure. He also pointed out that excision of the fistula caused a temporary increase in both systolic and diastolic blood pressures with a gradual adjustment to a more normal systolic level and a resultant decrease in pulse pressure. Holman² observed also that atropine prevents retardation in the heart rate when the fistula is closed. He concluded that the slowing of the heart rate was probably due to vagal stimulation, which occurs when the fistula is obliterated by compression and the increased blood pressure and blood volume distend the aorta. These studies did much to explain the observations made by Branham³ in 1890 that obliteration of the thrill over an arteriovenous fistula by manual compression produced a marked slowing of the heart rate. Lewis and Drury⁴ found a normal venous pressure and a decrease in the flow of blood through the arms and skin in certain patients with an arteriovenous anastomosis. They thought that the cardiac hypertrophy which occurs in this condition was due to a deficient coronary blood supply. They showed, however, that a rise in venous pressure and cardiac output occurred when the anastomosis was quite large. Since these observations were made, Holman⁵ has demonstrated that the degree of change in the general circulation of patients with an arteriovenous aneurysm is dependent on the size and duration of the fistula.

Ellis and Weiss⁶ lately reported studies of the circulation of two patients with recently acquired arteriovenous anastomosis. The communication in one of these patients was 3 mm in diameter and produced the classic signs of an arteriovenous fistula. No similar studies of a patient with a large fistula of long standing and advanced general circulatory changes have been reported.

2 Holman, Emile. The Physiology of an Arteriovenous Fistula, *Arch Surg* 7 64 (July) 1923.

3 Branham, Harris H. An Aneurism of the Femoral Artery Presenting a Strange and Unaccountable Phenomenon, *Internat J Surg* 2 250, 1890.

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METHOD

Following the method of Field, Bock, Gildea and Lathrop,⁷ twenty-three observations were made over a period of three months. These observations are divided as follows:

- (1) First period. Preoperative, patient resting in bed (six observations)
- (2) Second period. Thirteen days immediately after operation, patient resting in bed (six observations)
- (3) Third period. Two months after operation (eleven observations)
Recommunication of the fistula occurred during this time

From these studies the following values were derived: the cardiac output per minute and per beat, the carbon dioxide content of arterial and venous blood, the carbon dioxide transport per hundred cubic centimeters of blood or the arterio-venous difference of carbon dioxide, the respiratory minute volume, the carbon dioxide excretion per minute, respiratory rate, percentage of oxygen and carbon dioxide of the expired air, and the basal metabolism. All observations were made in the basal state with the patient in a semi-upright position.

RESULTS

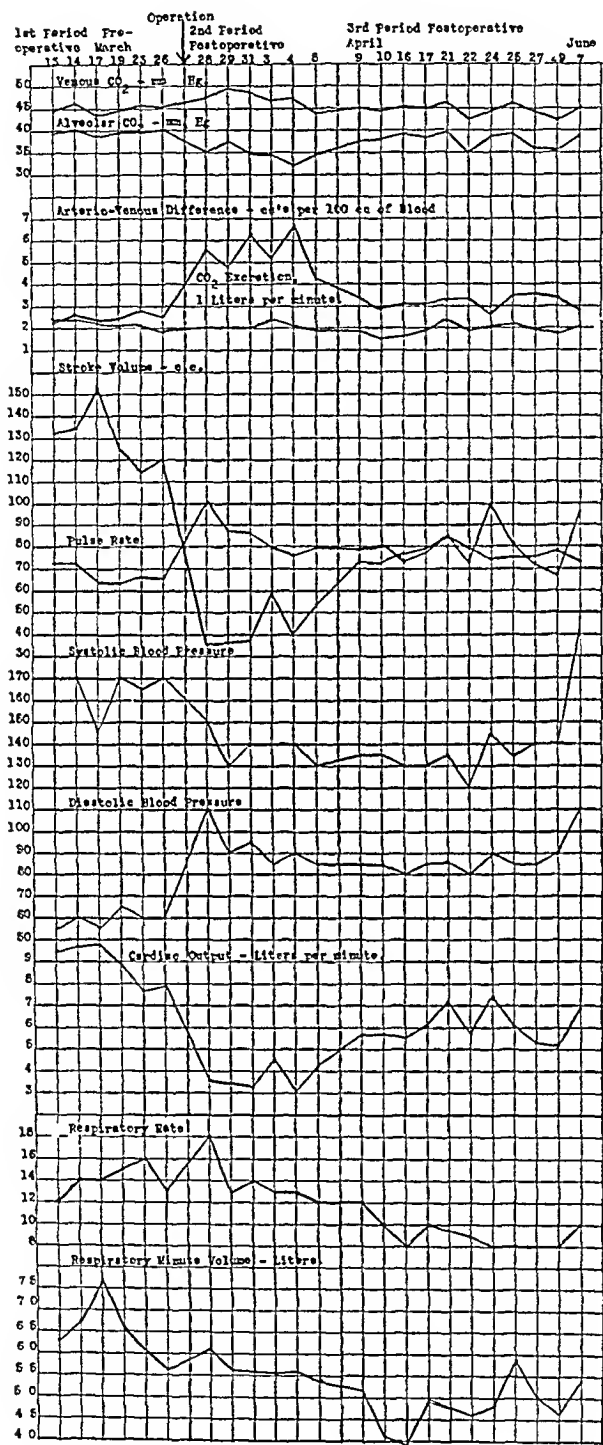
Cardiac Output—Six observations made before operation ranged between 9.8 liters a minute with a stroke volume of 154 cc. and 7.7 liters a minute with a stroke volume of 115 cc. The average of these observations was 8.95 liters a minute and 131 cc. a beat.

Studies were resumed the second day after operation and six observations were made during the second period or next thirteen days. A striking decrease occurred in the cardiac output from a preoperative level of 8.95 to 3.76 liters a minute, a reduction of 58 per cent. There was a corresponding drop in stroke volume from 131 to 45 cc., or 65 per cent. The second day after operation a light bruit could be heard over a small area medial to the incision. The bruit remained constant in its intensity during this period of study. No thrill was palpable.

In the third period of study, eleven observations were made over an interval of two months. During this period the bruit became more intense, and at the time of the last observation a definite thrill was felt over the area of incision. Obliteration of the thrill by manual pressure did not change the heart rate or blood pressure.

The average cardiac output in the third period of study was 6.77 liters a minute, an increase of 44 per cent over the immediate postoperative cardiac output of 3.76 liters a minute observed during the second period. The stroke volume increased from 45 to 75 cc., or 75 per cent. These observations paralleled the physical signs of the reestablishment of the arteriovenous communication.

⁷ Field, J. H., Bock, A. V., Gildea, E. F., and Lathrop, F. L. The Rate of the Circulation of the Blood in Normal Resting Individuals, *J. Clin. Investigation* 1: 65, 1924.



Graphic representation of the changes observed before and after operation

TABLE 1—All Observations Made Over the Entire Period of Study

Date, 1970	Arteriovenous			Cardiac			Blood Pressure		Pulse Pressure	Oxygen Con- sump- tion per Minute, Cc	Respi- ratory Quo- tient	Percent age of Oxygen Utili- zation of In- spired Air	Percent age of Carbon Dioxide Excretion of Ex- pired Air	Ventila- tion Liters per Minute	Comment
	Alveolar Percent Carbon Dioxide, Mm Hg	Venous Percent age of Carbon Dioxide, Mm Hg	Difference in Percent of Carbon Dioxide, per Cent by Volume	Output, Liters per Minute	Pulse Rate per Minute	Stroke Volume, Cc	Sys- tole Mm Hg	Diastole Mm Hg							
March 13	39.2	11.8	2.21	233	72	132	170	55	115	270	0.86	1.12	3.80	12	Before operation
March 14	40.5	16.9	2.62	235	72	135	170	60	110	301	0.85	1.16	3.79	11	Before operation
March 17	37.9	13.1	2.30	227	64	151	115	75	90					11	Before operation
March 19	30.3	14.9	2.5	211	63	126	170	65	105	200	1.01	1.00	3.11	15	Before operation
March 23	39.6	16.1	2.85	219	67	115	165	60	105	211	0.89	1.98	3.56	16	Before operation
March 26	40.5	46.3	2.18	198	66	121	170	60	110	211	0.77	1.55	3.18	13	Before operation
March 28	35.1	17.8	5.60	205	101	36	150	110	10	277	0.71	1.53	3.35	18	2 days after operation
March 29	37.8	49.6	1.75		87		130	90	10					13	3 days after operation
March 31	41.9	18.3	6.30	201	86	37	140	95	15	275	0.73	1.89	3.37	11	5 days after operation
April 3	31.5	16.2	5.26	216	79	59	140	85	55	245	0.83	1.28	3.56	13	8 days after operation
April 4	32.0	17.1	6.71	206	76	40	140	90	50	260	0.79	1.65	3.69	13	10 days after operation
April 8	31.2	11.0	1.37	185	79	51	130	85	45	215	0.86	3.95	3.99	12	11 days after operation
April 9	37.5	15.3	3.13	196	78	73	135	85	50	236	0.83	1.16	3.15	12	15 days after operation
April 10	37.7	11.1	2.91	166	80	72	115	85	50	206	0.81	4.12	3.57	10	16 days after operation
April 16	38.7	15.8	3.10	172	72	77	140	80	50	206	0.83	1.66	3.89	8	22 days after operation
April 17	37.9	45.0	3.10	190	78	79	130	85	15	234	0.81	4.28	3.46	10	23 days after operation
April 21	39.0	16.9	3.10	218	81	86	135	85	50	236				27 days after operation	
April 22	35.0	12.7	3.38	194	79	73	120	80	10	236	0.82	1.59	3.77	9	28 days after operation
April 24	38.3	11.6	2.72	202	71	100	115	90	55	233	0.87	1.89	3.80	8	30 days after operation
April 25	38.7	16.5	3.17	210	75	81	135	85	50	232	0.91	3.92	3.55	8	31 days after operation
April 27	35.9	11.1	3.62	196	75	72	140	85	55	221	0.89	4.35	3.86	8	33 days after operation
April 29	37.2	12.2	3.35	176	78	67	140	90	50	213	0.82	1.55	3.75	8	35 days after operation
June 7	38.1	15.2	2.89	201	73	95	195	110	95	275	0.75	5.11	3.72	10	10 weeks after operation

Blood Pressure—Before operation, the average blood pressure was 164 mm systolic and 59 mm diastolic, with a pulse pressure of 105 mm. Following operation, there was a drop of 16 per cent in the systolic pressure to 138 mm, while the diastolic pressure increased 56 per cent to 92 mm, a change in percentage almost equal to the decrease which occurred in the cardiac output. During the next ten observations, made over a period of one month while the patient was in the hospital, the blood pressure remained unchanged. After the patient was discharged from the hospital, the blood pressure increased to 195 mm systolic and 110 mm diastolic. Because of the sustained elevation of the diastolic pressure, it was thought that this change in blood pressure was a result of the coexistent arteriosclerosis and hypertension rather than of any change which occurred in the arteriovenous communication.

Thus it seems that the reestablishment of the fistulous communication did not cause any significant change in blood pressure even though there was an increase in the cardiac output. An explanation of this is not clear, but it confirms observations made previously⁸ that very little relation exists between blood pressure and cardiac output, even in the same person.

Heart Rate—Obliteration of the fistula by manual compression resulted in a 20 per cent decrease in the heart rate from 100 to 80 beats a minute. This decrease was accompanied by a considerable rise in both systolic and diastolic blood pressures.

The average heart rate before operation was 67 beats a minute. During the immediate postoperative period, the heart rate increased from 67 to 85 beats a minute, or 27 per cent. This increased rate was maintained throughout the remainder of the study, although there was a tendency for some decrease to occur as the fistulous communication became reestablished. These results are not in accord with those of Ellis and Weiss,⁶ who found a decrease in heart rate both when the fistula was temporarily closed by manual pressure and also following permanent closure by operation.

Vital Capacity—There was a gradual increase in the vital capacity from 2.4 to 4.1 liters extending over the entire period of observation. This increase was not directly related to any immediate change in the circulatory mechanism resulting from obliteration of the fistula but was probably due to improved circulatory efficiency, the result of prolonged rest in bed and closure of the fistula.

⁸ Burwell, C. Sidney, and Smith, Carter. The Output of the Heart in Patients with Abnormal Blood Pressures, *J. Clin. Investigation* 7 1, 1929.

Respiratory Rate and Minute Volume—The average respiratory rates during the first and second periods of study were 14 a minute. During the third period, the respiratory rate decreased to 9 a minute.

The respiratory minute volume was 6.54 liters before operation, 5.64 liters during the second period, and 4.97 liters during the third period or last two months of observation. Here again, the gradual decrease in respiratory minute volume was probably related to a general increase in circulatory efficiency rather than to any immediate alteration of the circulation by obliteration of the fistula.

Per Cent of Oxygen Utilization and Carbon Dioxide Excretion of the Expired Air—Coincident with the decrease in respiratory rate and minute volume there was an increase of 9.3 per cent in the amount of oxygen utilized from the inspired air and an increase of 3.6 per cent in the carbon dioxide content of the expired air. This same phenomenon occurs in patients recovering from cardiac failure,⁹ but is then accompanied by an increase in the carbon dioxide content of alveolar air. In this patient the alveolar air showed a decrease in the carbon dioxide content.

Oxygen Consumption and Carbon Dioxide Excretion—There was a gradual decrease in the patient's metabolic rate during his stay in the hospital. The oxygen consumption decreased 11 per cent and the carbon dioxide excretion 14 per cent. This was probably the result of prolonged rest in bed, as observations made after the patient was discharged from the hospital showed an increase in oxygen consumption to the level obtained when the patient was first observed.

Carbon Dioxide Tension of Arterial and Venous Blood—The carbon dioxide tension of the arterial blood estimated from alveolar air showed an average preoperative level of 39.5 mm of mercury. Immediately following operation it fell to an average of 34.8 mm of mercury, a decrease of 12 per cent. During the third period of study there was an abrupt rise to 37.5 mm of mercury, an increase of 7.7 per cent. This increased level of carbon dioxide tension in the arterial blood was maintained throughout the remainder of the study and was interpreted as one of the earliest and most definite signs of a recommunication of the arteriovenous communication.

There was an average carbon dioxide tension of 45.5 mm of mercury in the venous blood before operation. Following operation during the second period of study, there was an average increase to 47.1 mm.

⁹ Peters, J. P., Jr., and Barr, D. P. Studies of the Respiratory Mechanism in Cardiac Dyspnea. 1. Low Alveolar Carbon Dioxide of Cardiac Dyspnea, *Am J Physiol* **54**: 307, 1920. 2. Effective Ventilation in Cardiac Dyspnea, *ibid.*, p. 345.

of mercury, or 3.5 per cent, a much smaller change than that which occurred in the arterial level of carbon dioxide tension. During the third period of study when a recommunication of the fistula occurred, there was an increase to 44.8 mm of mercury, or 4.7 per cent. This was quite similar to the level of carbon dioxide in the venous blood before operation.

Carbon Dioxide Transport—The amount of carbon dioxide given off in the lungs by 100 cc of blood was 2.47 per cent by volume before the operation. Immediately following operation or during the second period of study, there was an average increase to 5.49 per cent by volume, or a change of 122 per cent. Interpreted in terms of oxygen transport or the coefficient of utilization, this represents a remarkable increase in circulatory efficiency. More than twice as much oxygen was being utilized from 100 cc of blood, and the tissue supply of oxygen was adequate, even though there was a decrease of 58 per cent in the cardiac output.

As the arteriovenous fistula became reestablished, there was a decrease in the carbon dioxide transport to 3.21 per cent by volume, a reduction of 42 per cent. This decrease in the coefficient of utilization was accompanied by an increase of 44 per cent in the cardiac output and represented a great decrease in circulatory efficiency.

The variations in the arteriovenous difference of carbon dioxide (carbon dioxide transport) that accompanied the changes in cardiac output were represented largely by fluctuations in the arterial level of this gas, while the venous carbon dioxide remained relatively constant. This is in accord with observations made previously¹⁰ that pathologic variations in the circulatory minute volume show the change in the carbon dioxide transport to be represented largely by a fluctuation in the arterial level of this gas. In physiologic variations of the cardiac output, as produced by exercise, for example, the change in the carbon dioxide transport is represented largely by a change in the venous level of this gas, while the arterial level remains quite constant.

COMMENT

The results of this study show that an arteriovenous fistula can greatly impair the efficiency of the circulation by causing an increase in the cardiac output and a decrease in the coefficient of utilization. This

10 Smith, W. C., Walker, G. L., and Alt, H. L. The Cardiac Output in Heart Disease. 1. Complete Heart Block, Auricular Fibrillation before and after the Restoration to Normal Rhythm, Subacute Rheumatic Fever and Chronic Rheumatic Valvular Disease, *Arch. Int. Med.* **45**:706 (May) 1930, 2. Effect of Exercise on the Circulation in Patients with Chronic Rheumatic Valvular Disease, Subacute Rheumatic Fever and Complete Heart Block, *ibid.* **45**:958 (June) 1930.

TABLE 2—*The Averages in Preoperative and Postoperative Observations*

Date	Num ber of Obser- vations	Alveolar		Venous		Arterio- venous Differ- ence in		Percent age of Carbon Dioxide, % by Volume	Carbon Dioxide Expired, per Minute, Cc	Cardiac Output, Liters per Minute	Pulse Rate per Minute	Stroke Volume, Cc	Blood Pressure			Pulse Pres- sure Cc	Oxygen Con- sump- tion per Minute, Cc	Respi- ratory Quo- tient	Percent age of Oxygen Utiliza- tion of Inspired Air	Percent age of Carbon Dioxide Excre- tion of Expired Air	Res- pira- tions per Minute	Ventila- tion, Liters per Minute	Vital Capac- ity, Liters
		Percent age of Carbon Dioxide, Mm Hg	Percent age of Carbon Dioxide, Mm Hg	Percent age of Carbon Dioxide, Mm Hg	Percent age of Carbon Dioxide, Mm Hg	Sys- tole, Mm Hg	Dias- tole, Mm Hg						Dias- tole, Mm Hg										
13 days before oper- ation	6	39.5	45.5	45.5	2.47	2.47	224	8.95	67	131	164	59	105	254	0.88	1.08	3.55	11	6.51	3.1			
First 13 days after operation	6	31.8	47.1	47.1	5.49	5.49	208	3.76	85	45	138	92	46	251	0.81	1.16	3.57	11	5.65	3.5			
Next 2 months after operation	11	37.5	44.8	44.8	3.21	3.21	195	6.77	77	79	139	88	56	226	0.84	1.14	3.68	9	1.97	3.99			

fact has previously been demonstrated in experimental animals by Holman and others. That cardiac failure may be a result of this decreased circulatory efficiency is also well known.

The studies recently reported by Ellis and Weiss⁶ illustrate the immediate effects of a recently acquired arteriovenous fistula on the circulation. The observations reported in this paper show the secondary circulatory effects of a fistula of long standing. A comparison of these two studies is of interest.

The arteriovenous fistula in the patient treated by Ellis and Weiss was 3 mm in width and produced the classic signs of this condition, i.e., increased pulse pressure, increased heart rate and Branham's phenomenon. The communication was, however, of only one month's duration, and there was no evident peripheral vascular damage. No change occurred in the cardiac output before or after operation.

In my patient there was a demonstrable reduction of 58 per cent in the cardiac output following operative closure of the fistula. The arteriovenous communication was of six years' duration, the peripheral vascular damage was marked and two periods of congestive heart failure had occurred.

The difference in my results and those of Ellis and Weiss are possibly due to the duration of the arteriovenous fistula and the resulting peripheral vascular changes.

It seems that in some instances, as shown by Ellis and Weiss, even though the communication is quite large, the peripheral vascular bed is capable of adjusting the circulation so that normal efficiency is still maintained. This circulatory adjustment of the capillary bed is probably a centrally controlled function. With the occurrence of general damage to the peripheral vascular bed, as demonstrated by my patient, this compensatory function is lost, the cardiac output increases and there is a decrease in circulatory efficiency.

SUMMARY

A measure of the cardiac output and related values was undertaken before and after operation in a person with a large arteriovenous communication of six years' duration and with secondary cardiovascular changes.

A reduction of 58 per cent in cardiac output and an increase of 122 per cent in the coefficient of utilization occurred following operative closure of the fistula. There was a gradual recommunication of the fistula after operation. This resulted in an increase in the cardiac output and a decrease in the coefficient of utilization.

REPORT OF A CASE

History—M H, a colored male laborer, aged 40 years, was admitted to the Emory University Division of the Grady Hospital on Feb 2, 1930, and discharged on April 17, 1930. Six years before admission to the hospital he was shot through the left groin with a pistol. He was sent to a hospital at that time and remained there six weeks. When discharged, he was told that he had an arteriovenous aneurysm. Four weeks after discharge, he began to experience shortness of breath and swelling of the feet and legs. This became so severe that he was forced to seek readmission to the hospital, where he remained for eight weeks. He was discharged feeling quite well. The Wassermann reaction of the blood was strongly positive at that time and he was given antisyphilitic treatment as long as he remained in the hospital.

He was able to work for one year and a half as a laborer, then the symptoms of cardiac failure returned, and he was readmitted to the hospital for a period of five weeks. At the end of this time, he returned to work and was free from symptom for about three and a half years.

He was first seen in this clinic in January, 1930. At this time he had a moderate degree of cardiac failure for which he was treated. He failed to respond to treatment, however, and was admitted to the hospital the next month.

There was a history of a penile lesion in 1918. He received only local treatment at that time.

Physical Examination—The patient was moderately dyspneic and orthopneic. There was no detectable cyanosis. Ophthalmoscopic examination showed normal disks, but the retinal arteries were moderately sclerosed. The jugular veins were moderately distended and there was visible pulsation of the great vessels of the neck. The respiratory rate was 22 per minute, the lungs were clear except for a few medium moist râles at the bases posteriorly. The heart was greatly enlarged. The apex impulse was diffuse and heaving in the fourth, fifth and sixth interspaces extending out into the anterior axillary line. The cardiac dulness was 13.5 cm to the left, 5 cm to the right with a supracardiac dulness of 6 cm. The first sound at the apex was accentuated and partially replaced by a systolic murmur. There was a gallop rhythm at a rate of 120 beats a minute. The aortic second sound was accentuated and of impure quality. The radial vessels were moderately sclerosed. The blood pressures were as follows: right arm, 200 mm systolic and 90 mm diastolic, left arm, 210 mm systolic and 90 mm diastolic, right leg, 270 mm systolic and 90 mm diastolic, left leg, 160 mm systolic and 50 mm diastolic.

Following manual compression and obliteration of the fistula in the left femoral region, the blood pressure in the right arm increased to 240 mm systolic and 100 mm diastolic. This increase was maintained for about four minutes and then began to return to its previous level. There was a simultaneous slowing of the heart rate from 100 to 80 a minute.

The abdomen was moderately distended, the liver could be felt 6 cm below the costal border. There was a small amount of free fluid in the abdomen.

In the left inguinal region there was a small pulsating mass about 3 cm in width and 6 cm in length. There was a continuous thrill and bruit over this mass, which could be obliterated by manual pressure.

There was moderate pitting edema of both legs. The superficial veins around the arteriovenous anastomosis were dilated, and there was a definite increase in the skin temperature of that area. Dorsalis pedis pulsations were easily felt in both feet.

Laboratory Examinations—The urinalysis was negative the blood count was normal both before and after operation. The blood chemistry was normal, but the Wassermann reaction of the blood was strongly positive. A teleoroentgenogram at the time of admission showed an aortic shadow of 5 cm, the left margin was 13 cm, the right margin 5 cm, with a transverse thoracic diameter of 28 cm. A second plate made one month after operation showed a definite decrease in the heart shadow. The measurements at that time were 11.5 cm to the left, 4.5 cm to the right, the aortic shadow was 6 cm and the transverse diameter of the chest, 29 cm.

Clinical Course—The patient was given digitalis and antisyphilitic treatment by mouth. There was a rapid subsidence of the edema and of the shortness of breath. By the end of the first week in the hospital he was free from edema and could lie flat in bed without discomfort. The vital capacity had increased from 24 to 31 liters. The blood pressure was 160 mm systolic and 80 mm diastolic.

Two weeks after admission, the patient was well compensated. The lungs were clear throughout, and there was no peripheral edema. The vital capacity was 34 liters, respirations were 12 a minute, the heart rate was 72 a minute and the blood pressure was 170 mm systolic and 55 mm diastolic. Studies of the cardiac output and related values were begun at this time.

Four weeks after the patient was admitted to the hospital, Dr J. L. Campbell performed a quadruple ligation of the femoral and deep femoral arteries and veins. It was impossible to isolate the direct communication between the artery and vein, and its actual size could not be determined. There was considerable dilatation of the adjacent veins.

The day after operation, the patient's general condition was good. There was no difference in the skin temperature of the legs. The blood pressure was 195 mm systolic and 115 mm diastolic. The heart rate was 80 a minute with an occasional premature beat. No thrill or bruit was found over the site of operation. The second day after operation, the patient was able to sit up in bed. A measure of the cardiac output was done in this position. The fourth day after operation, a faint bruit but no thrill was detected over a small area medial to the incision. This bruit could be heard over a wider area and was more intense during the remainder of his stay in the hospital. The patient remained in bed three weeks and repeated observations of the cardiac output were made during this time. He was discharged nine weeks after admission and was not seen again for seven weeks. At this time a definite thrill and bruit were found over the left femoral region. These could be obliterated by pressure, but there was no change in the heart rate or blood pressure. He was free from symptoms, and the vital capacity was 41 liters. Observations of the cardiac output were repeated at this time. He was seen again five months later. The physical signs were unchanged, and he was capable of performing light work without discomfort.

MALIGNANT NEPHROSCLEROSIS

PATHOGENESIS

PHILLIP F SHAPIRO, M D

CHICAGO

In primary arterial hypertension the essential renal lesion is nephrosclerosis. In most cases, the nephrosclerosis is in itself benign. The chronic hypertension terminates in cardiac insufficiency, in a cerebrovascular accident, in a coronary accident or through some incidental cause. In the remaining cases, the nephrosclerosis itself is the malignant, lethal factor, and the hypertensive state is closed by uremia.

In most cases the clinical and morphologic distinction between benign and malignant nephrosclerosis is sharp. The group of chronic hypertension that ends through some factor other than renal insufficiency almost always presents the well defined histologic picture of simple renal arteriosclerosis. The group that ends in uremia is usually associated with a marked and abrupt, but just as well defined, change in the histologic picture. Transitions are scanty, and so striking are the morphologic differences that in their original presentation of the subject, Volhard and Fahr¹ postulated the addition of an altogether different etiology and pathogenesis for the malignant form. They regarded the new histologic changes as inflammatory rather than sclerotic. They conceived that benign nephrosclerosis turned into a malignant form and ended in uremia, when a toxic-irritative or inflammatory factor was imposed on the predisposing arteriolosclerosis.

The existence of such an inflammatory-sclerotic combination form was hotly contested by other investigators. Lohlein,² in particular, firmly insisted that malignant nephrosclerosis was but another form of benign sclerosis, both conditions were arteriolosclerotic, the same in etiology and in pathogenesis and differed only in the "tempo" of development. As far as renal function was concerned, slow arteriosclerosis of the kidneys was benign. The slow decrease in the glomerular blood supply led to the characteristic hyaline and atrophic changes,

¹ Submitted for publication, Oct 31 1931

² From the Department of Pathology, Cook County Hospital

1 Volhard, F, and Fahr, T. Die Brightsche Nierenkrankheit, Berlin, Julius Springer, 1914

2 Lohlein, M. Ueber Schrumpfnieren, Beitr z path Anat u z allg Path **63** 570, 1917, Zur Nephrocirrhosis arteriolosclerotica, Med Klin **14** 136, 1918. Zur vascularen Nierensklerose, *ibid* **12** 1042, 1916, Zur Pathogenese der vascularen Schrumpfniere, *ibid* **12** 741 and 872, 1916, Erwiderung auf T. Fahr's Aufsatz, Zentralbl f Path u path Anat **28** 209, 1916

but did not appreciably impair renal function. Similar but more rapidly developing arteriosclerosis brought with it an abrupt glomerular ischemia, which led to more intense histologic changes and to death in uremia. The process was the same, only faster, and no new toxic factor had to be invoked.

Jores,³ too, believed that there was no fundamental difference between the two forms. He emphasized the diffuse involvement of the finest vessels in malignant nephrosclerosis as compared with the focal involvement and the predominant sclerosis of the larger vessels in the benign form. Fishberg,⁴ Stein,⁵ Murphy and Grill⁶ and the majority of authors agreed with Lohlein that both forms were sclerotic. In the malignant form there was no added inflammatory factor, but only an acceleration of the same sclerosis. In a recent, extensive study of 420 cases of primary arterial hypertension, including 36 cases of death in uremia, Bell and Clawson⁷ pointed out that when the uremia had developed slowly, the renal changes were those of simple sclerotic atrophy. They found that rapidly developing uremias were associated with the more severe changes of malignant nephrosclerosis. They ascribed these changes only to more abrupt arterial occlusion and not to any added toxic factor.

Meyer⁸ Steinberg,⁹ Ask-Upmark¹⁰ and others, however, could never reconcile themselves to the view that the changes in malignant nephrosclerosis were merely sclerotic.

The malignant forms were found especially in younger patients in whom there should be least sclerosis. The changes were so widely different from those of benign sclerosis, and they resembled the changes of focal nephritis and of periaortitis nodosa so closely, that it forced

3 Jores, L. Ueber die Arteriosklerose der kleiner Organarterien und ihre Beziehungen zur Nephritis, *Virchows Arch f path Anat* **178** 367, 1904.

4 Fishberg, A. M. Anatomic Findings in Essential Hypertension, *Arch Int Med* **35** 650 (May) 1925, The Arteriolar Lesions of Glomerulo-Nephritis, *ibid* **40** 80 (July) 1927.

5 Stern, M. Ueber einen besonders akut verlaufenen Fall von Arteriolenekrose der Nieren, *Virchows Arch f path Anat* **251** 718, 1924.

6 Murphy, F., and Grill, J. So-Called Malignant Hypertension. A Clinical and Morphologic Study, *Arch Int Med* **46** 75 (July) 1930.

7 Bell, E. T., and Clawson, B. J. Primary Hypertension, *Arch Path* **5** 939 (June) 1928.

8 Meyer, O. Ueber das Vorkommen und die Bedeutung entzündlicher Gefassveränderungen in den Nieren, *Verhandl d deutsch path Gesellsch* **19** 352, 1923.

9 Sternberg, B. Thrombo-Angioneurotic Changes of the Kidneys in Chronic Nephritis, *Arch Int Med* **44** 272 (Aug.) 1929.

10 Ask-Upmark, E. Ueber juvenile maligne Nephrosklerose und ihr Verhältnis zu Störungen in der Nierenentwicklung, *Acta path et microbiol Scandinav* **6** 383, 1929.

the impression of a superimposed toxic element Fahr, especially, maintained that sclerotic ischemia could never account for the proliferative and other changes seen in the malignant forms, and that an added inflammatory or toxic element would have to be accepted¹¹

In the long controversy that has been waged over the etiology and pathogenesis of malignant nephrosclerosis, numerous bitter polemics have been exchanged, an extensive literature has developed and a large amount of critical observation and experimentation has been stimulated Herxheimer¹² finally suggested in this argument that questions of etiology had not been sufficiently separated from those of pathogenesis As long as nothing definite was known (and nothing definite is yet known) about the etiology of either the benign or the malignant forms, their etiologic separation or identification was only a matter of the subjective opinion of the individual investigator So far, only their respective pathogeneses could be studied and compared and questions of etiology should be avoided until something more definite was known He agreed with Fahr in the recognition of the fact that aside from a high grade, slow arteriolosclerosis, there were other arteriolar changes that could lead much more rapidly to uremia Herxheimer pointed out that these changes were different from those of benign sclerosis, but he did not believe them to be of inflammatory origin

At first Volhard had been led to assume a toxic basis for the malignant changes, because of their resemblance to nephritis But with his conception that the pathogenesis of nephritis was based on glomerular ischemia, he conceded that malignant nephrosclerosis might also be only ischemic in origin, an accelerated form of benign nephrosclerotic ischemia He therefore relinquished his original position with Fahr on this subject He attributed the onset of the renal insufficiency to a general and renal vasoconstriction, with abrupt glomerular capillary spasm Severe glomerular ischemia led to the degenerative and reactive proliferative changes seen in the malignant forms¹³

11 Fahr, T Ueber atypische Befunde aus den Kapiteln des Morbus Brightii nebst anhangswisen Bemerkungen zur Hypertoniefrage, Virchows Arch f path Anat **248** 323, 1924, Pathologische Anatomie des Morbus Brightii, in Henke and Lubarsch Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol 6 Ueber Nephrosklerose, Virchows Arch f path Anat **226** 119, 1919, Ueber maligne Nierensklerose (Kombinationsform), Zentralbl f Path u path Anat **27** 481, 1916, Ueber die Beziehungen von Arteriosklerose, Hypertonie und Herzhypertrophie, Virchows Arch f path Anat **239** 41, 1922, Kurze Bemerkungen zur Frage der malignen Nierensklerose, Zentralbl f Path u path Anat **28** 408, 1917

12 Herxheimer, G Niere und Hypertonie, Verhandl d deutsch path Gesellsch **15** 211, 1912, Ueber Arteriolonekrose der Nieren, Virchows Arch f path Anat **25** 709, 1924

13 Volhard, F Der arterielle Hochdruck, Verhandl d deutsch Gesellsch f inn Med **35** 134, 1923

It was objected that the cause of the glomerular ischemia could not lie in capillary spasm. Capillary spasm should produce the most marked ischemic changes distal to the glomerulus, whereas they were often seen only proximal to the glomerulus in the afferent arteriole and not in the glomerulus. The cause of the glomerular ischemia must therefore lie somewhere proximal to the glomerulus.

Klemperer and Otani were struck with the fact that glomerular changes identical with those of malignant nephrosclerosis could be found in the periphery of recent, aseptic, renal infarcts. They declared: "Here, there could be no doubt as to the ischemic nature of these changes." They maintained with Volhard that benign nephrosclerosis and malignant nephrosclerosis were essentially the same and that both were ischemic. But they traced the origin of the glomerular changes in the malignant form, not to capillary spasm, but to thrombotic or proliferative occlusion at some point in the corresponding afferent arterioles.¹⁵ They demonstrated these occlusions by painstaking serial sections.

The un.injected kidney, however, is not altogether reliable material from which to study the vascular condition of that organ. Sjoval¹⁶ fixed kidneys by the ordinary immersion in formaldehyde, as well as by injecting formaldehyde into the renal artery. He demonstrated great discrepancies between the histologic pictures of the injected and those of the un.injected specimens. Vessels that were apparently occluded by thrombi or proliferation in the un.injected specimens were widely patent in the injected ones. Gustav Ricker's observations, which were made directly on the living animal, also strongly emphasized that many of the histologic pictures that have been accepted as ischemic were only agonal or postmortem artefacts.¹⁷

In view of the foregoing investigations, a study was attempted of the nephrosclerotic material available from 1,000 consecutive autopsies performed at the Cook County Hospital on patients over 20 years of age. An injection method was used to check the direct observations. In the course of this study, certain histologic changes attracted attention, which amplified the transition between benign and malignant nephrosclerosis. Analyzed on the basis of Ricker's views, they identified the benign and malignant forms, whatever their respective etiologies.

14 Reference deleted by author

15 Klemperer, P., and Otani, S. Studies on Malignant Nephrosclerosis, personal communication. Studies on Malignant Sclerosis of the Kidneys, *Arch Path* 8:559 (Sept.) 1929.

16 Sjoval, E. Ueber die anatomischen Formen der Nephrosclerose, *Acta med Scandinav* 65:484, 1927.

17 Ricker, Gustav. Sklerose und Hypertonie der innervierten Arterien, Berlin, Julius Springer, 1927.

may have been, in a single pathogenesis. They offered for both a single hemodynamic mechanism, which, however, is not as commonly accepted ischemic, but which is a form of hyperemia with retardation.

STATISTICAL STUDY

Among the 1,000 autopsies, there were altogether 171 cases of nephrosclerosis, 36 with uremia and 135 without uremia. In 47 per cent (80 cases) of the entire series, the chronic hypertension terminated in cardiac decompensation, in 9 per cent (16 cases) by a coronary accident, in 19 per cent (32 cases) by a cerebral vascular accident, in 4 per cent (7 cases) through some incidental cause and in 21 per cent (36 cases) in uremia.

In the large, extra-uremic, so-called "benign" group, eighty-six patients, or 64 per cent, were over 50 years of age and forty-nine patients, or 36 per cent, were under 50 years of age. Seventy-one per cent of Klemperer and Otani's patients were over 50. Forty-five cases, or 33 per cent, occurred in women, and ninety cases, or 67 per cent, in men. This ratio is practically the same as the relative proportion of autopsies performed on men and on women, 30 and 70 per cent, respectively, in the entire series. Therefore, men were affected as commonly as women.

Fifty (37 per cent) of the 135 cases occurred in colored patients, and 85 (63 per cent) in white patients. This percentage is exactly the same as that obtained at the Cook County Hospital in the entire series of 1,000 cases. Thus colored patients were affected as commonly as white. Therefore, there was no special sexual or racial predisposition toward benign nephrosclerosis. Forty-one cases (30 per cent) occurred in syphilitic patients, and 94 cases (70 per cent) occurred in nonsyphilitic patients. Judged by the characteristic changes in the aorta, of the entire 1,000 patients only 17 per cent were syphilitic. In the series of nephrosclerotic patients, 21, or 42 per cent, of the 50 colored patients were syphilitic. Nineteen, or 22 per cent, of the 85 white patients were syphilitic. This relative proportion is about the same as that for syphilis in colored and white patients (2:1) in the entire 1,000 autopsies. It can be concluded that as far as the material from the Cook County Hospital demonstrates, syphilis is almost twice as frequent in patients with benign nephrosclerosis as it is in those who do not have nephrosclerosis, and the importance of the syphilitic factor is the same in the colored as in the white patients.

Of the thirty-six patients who died of uremia, twenty-five, or 69 per cent, were less than 50 years of age, while eleven, or 21 per cent, were over 50. In Klemperer and Otani's patients, 75 per cent were under 50 years of age. This slight difference in percentage arises only

from the slightly different type of material which is included in the uremic series in this paper. With the same type of cases that Klemperer presented, the proportion of cases at the Cook County Hospital in which the patients were under 50 years of age is the same. 74 per cent Klemperer and Otani found that the average age of women was 44 years, of men, 30. In this series, even when the results were corrected for the difference in the type of case, the average age for both men and women was the same, 46 years.

Twelve, or 33 per cent, of the uremic patients were syphilitic, twenty-four, or 67 per cent, were nonsyphilitic. This proportion was the same as that found in benign nephrosclerosis. Of these twelve patients, seven were colored and five were white, this too was about the same relative proportion as that found for syphilis in benign sclerosis. The syphilitic factor here too was the same in the colored patients as in the white ones. It could be concluded that syphilis predisposes to nephrosclerosis in general, but no more to the malignant form than to the benign.

Twenty-six, or 72.3 per cent, of the cases occurred in colored persons, and 10 cases, or 27.7 per cent, in white patients. Since in the entire 1,000 autopsies only 36.5 per cent occurred in colored patients the incidence of nephrosclerosis with uremia was twice as frequent in the colored as in the white group. In benign nephrosclerosis, the incidence in both races was equal for the racial proportion of cases was the same as in the entire 1,000 cases. Therefore, while there is no racial predisposition to benign nephrosclerosis, there is a distinct predisposition of the colored race to nephrosclerosis with uremia.

Seventeen, or 47 per cent, of the cases occurred in women, nineteen or 53 per cent, in men. In the entire series, only 30 per cent occurred in women. Corrected for this general percentage, the proportion of men to women in malignant nephrosclerosis was 1.24, while in benign nephrosclerosis the proportion was 1.1. Therefore, there is a distinct predisposition of the female sex to malignant nephrosclerosis, while no such predisposition exists to the benign form.

CLINICAL AND MORPHOLOGIC STUDY

Among the thirty-six cases of nephrosclerosis with uremia, in only one had the uremia been induced by simple progressive shrinking of the substance of the kidney until there was not enough of it left to support life (case 35, table 1). In this case practically every glomerulus was partly or completely hyalinized or was involved in pericapsular fibrosis.¹⁸

18 McGregor, L. Histological Changes in the Renal Glomerulus in Essential Hypertension, *Am J Path* 6:347, 1929.

Hardly a normal glomerulus was found. This type of termination is rare, because the sclerosis is slow and because the nephrosclerotic patient is in a constant, precarious state from many other renal and extrarenal vascular dangers. Before the kidney shrinks to a point incompatible with life, the slow sclerotic process is usually stopped abruptly by cardiac failure, a cerebral vascular accident, a coronary accident or through some incidental cause. Long before marked renal atrophy has occurred, the prolonged strain of maintaining high blood pressure and the vascular changes in the myocardium sometimes lead to cardiac decompensation, which even of itself may not be fatal, but which precipitates uremia by abruptly aggravating the renal circulatory embarrassment.¹⁹ There were four such cases in this series. In three (cases 33, 34 and 35) a moderate degree of renal atrophy had been reached. About 35 per cent of the glomeruli were partly or completely hyalinized, about 25 or 30 per cent were involved in pericapsular fibrosis and shrinking. The remaining 30 or 35 per cent were unchanged, except as they showed some degree of capillary dilatation. A marked degree of capillary dilatation was prominent in the intertubular capillaries of these kidneys, as a sign of the cardiac passive congestion that had precipitated the fatal renal insufficiency. In one case (case 36) the predisposing renal sclerosis had advanced but slightly when the kidneys were thrown out of function and uremia was precipitated by passive congestion.

The majority of the cases ending in uremia, thirty-one of thirty-six, did not show enough renal atrophy or enough passive congestion to account for the renal failure. The uremic issue was determined by an altogether different type of renal change. Twenty-three of the cases answered Fahr's classic description of malignant nephrosclerosis.

Clinical Picture—The usual clinical picture was that of chronic hypertension of long duration in patients less than 50 years of age, the condition occurred in women more commonly than in men and in colored patients more commonly than in white ones. There was no history of previous nephritis. The patients had usually been robust and sturdy and often had engaged in hard manual labor until a short time before admission. In most cases the duration of the antecedent hypertensive phase could not be accurately determined. Some of the patients had known that they had had a high blood pressure for from six months to ten years, other patients were totally unaware of it until the time of admission. Whenever noted, the hypertension was almost always found to be constant and exceedingly high. Often the condition was symptomless, at other times it was associated with headaches, weakness, ner-

¹⁹ Baehr, G., and Ritter, S. A. The Arterial Supply of the Kidney in Nephritis, *Arch Path* 7:458 (March) 1929.

TABLE 1—*Nephrosclerosis with Uremia*

Post mortem No	Color	Sex	Age	Anatomic Signs of Uremia		Weight of Kidneys, Gm	Weight of Heart, Gm	Syphilitic Aortitis	Contributory Cause of Death	Clinical Impression	Duration	Blood Chemistry	Blood Pressure	Kahn Test	Histologic Observations
				Uremia	+	Uremia	+								
1	340	C	M	22	+	225	530	—		Uremia	2 wks	Creatinine 10 urea nitrogen 100	228/110	—	Necrosis
2	578	C	M	38	+	294	680	—		Uremia	2 wks	Urea nitrogen 137 creatinine 8.6	198/140	—	Necrosis
3	804	C	F	78	+	260	490	—		Uremia		Urea nitrogen 162 creatinine 9.2	232/118	—	Necrosis
4	378	C	F	49	+	260	480	—		Malignant hypertension	1 wk	Urea nitrogen 87 indican 4+	260/162	—	Necrosis
5	771	C	M	24	+	160	800	—		Bacterial endocarditis	3 wks	Indican 4+	246/176	—	Necrosis
6	798	C	M	78	+	280	465	—		Cardiorenal disease	1 wk	Urea nitrogen 173	240/180	—	Necrosis
7	579	C	M	60	+	340	455	—		Uremia	3 wks	Urea nitrogen 103	270/210	—	Necrosis
8	594	C	M	30	+	310	630	—		Uremia	3 mos	Indican 3+	230/180	—	Necrosis
9	942	W	M	41	+	160	475	—	Cerebral hemorrhage	Cardiorenal disease		Indican 3+	220/170	—	Necrosis
10	82	C	F	65	—	240	405	—		Bronchopneumonia	2 mos	Urea nitrogen 90 indican 1+	128/ 60	—	Necrosis
11	129	C	F	38	—	300	518	—		Uremia	2 mos	Urea nitrogen 151 creatinine 8	198/128	—	Necrosis
12	396	W	F	65	+	170	325	+		Chronic nephritis	3 wks	Indican 3+	278/100	—	Necrosis
13	539	W	F	49	+	320	500	+		Uremia	2 mos	Urea nitrogen 117	235/110	—	Necrosis
14	742	C	M	61	+	220	515	+	Hemorrhage from acute peptic ulcer	Uremia	2 mos	Urea nitrogen 96 creatinine 7	220/150	—	Necrosis
15	899	W	M	47	+	315	706	—	Bronchopneumonia	Uremia	7 wks	Urea nitrogen 75 creatinine 6.6	260/170	—	Necrosis
16	360	C	F	60	+	150	420	—		Uremia	2 wks	Indican 1+	198/106	—	Necrosis, arteriolar only
17	623	W	M	55	+	260	635	—	Cerebral hemorrhage	Undetermined	died 5 min after admission				Necrosis, arteriolar only
18	775	C	F	78	+	120	505	—		Uremia	2 mos	Indican 4+	1230/110	—	Necrosis, arteriolar only

19	480	W	F	46	+	290	460	+	Uremia	1 wk	Urea nitrogen 114	198/142	—	Necrosis, arteriolar only
20	15	W	F	91	+	380	710	—	Uremia	7 wks	Urea nitrogen 178	240/120	—	Necrosis with peri arteriolitis
21	917	C	F	44	+	190	510	+	Uremia	3 wks	Urea nitrogen 135, creatinine 11	260/180	—	Necrosis with peri arteriolitis
22	401	C	M	42	+	200	775	—	Miliary tuberculosis	2 wks	Urea nitrogen 107	174/118	—	Necrosis, miliary tubercles
23	731	C	F	31	—	280	395	—	Pyelonephritis	2 mos	Urea nitrogen 15 1 wk before death	280/150	—	Necrosis, pyelonephritis
24	324	C	M	53	+	200	610	—	Broncho pneumonia	2 mo	Impending uremia	268/176	—	Prestasis only, no necrosis
25	240	C	M	16	+	225	385	—	Peritonitis	2 wks	Undetermined	—	—	Prestasis, necrosis slight
26	338	C	M	11	+	200	150	—	Broncho pneumonia	2 wks	Hypertensive heart disease	250/140	—	Prestasis, necrosis slight
27	350	C	M	34	+	390	750	—	Impending uremia	2 mos	Urea nitrogen 105	234/152	—	Prestasis, necrosis slight
28	385	C	M	39	+	240	560	+	Broncho pneumonia	3 wks	Indican 4+	216/148	—	Prestasis, necrosis slight
29	503	W	F	35	+	160	615	+	Broncho pneumonia	3 wks	Indican 4+	216/148	—	Prestasis, necrosis slight
30	701	W	M	59	+	110	360	—	Coronary thrombosis	4 mos	Indican 4+	228/130	—	Prestasis, necrosis slight, marked atrophy
31	270	C	F	55	+	145	465	+	Hypertensive heart disease	2 wks	Indican 4+	288/176	+	Prestasis, no necrosis marked atrophy
32	671	W	M	49	+	115	480	—	Cardiac de compensation	1 mos	Urea nitrogen 42	210/140	—	No prestasis, no necrosis, passive congestion, marked atrophy
33	551	C	F	64	+	140	625	—	Impending uremia	—	Indican 4+	220/110	—	No prestasis, no necrosis, passive congestion, marked atrophy
34	127	C	M	52	+	175	460	—	Impending uremia	1 mo	Urea nitrogen 58	215/130	—	No prestasis, no necrosis, passive congestion, marked atrophy
35	769	C	F	38	+	170	350	—	Broncho pneumonia	—	Urea nitrogen 184, creatinine 10.5	170/110	—	No prestasis, no necrosis, no congestion marked atrophy
36	98	C	M	50	+	220	575	+	Hemorrhage from peptic ulcer, passive congestion	4 mos	Urea nitrogen 112, creatinine 8.7	180/130	—	No prestasis, no necrosis, no atrophy, passive congestion

vousness, slight nocturia or visual disturbances, which dragged on for from six weeks to months but which afforded no great disability to the patient. Frequently the patients were admitted with the complaints that for the last two months the symptoms had become markedly worse, with severe headaches, marked visual disturbance or cardiac insufficiency. Some cases, however, had passed abruptly into the terminal state without warning. In others, the patients dropped so quickly into coma that no history could be obtained.

The terminal uremic state was rapid, progressive and relentless. In a patient with chronic nephritis, uremic symptoms might develop and the patient might recover temporarily. In the cases of nephrosclerosis with uremia no remissions were noted once the uremic symptoms had begun. In many cases the duration of the major presenting symptoms was difficult to ascertain. The average duration is estimated at five or six weeks, with a range of variation of from one week to four months. Klemperer and Otam observed an average duration of the period of renal insufficiency of thirty-two days.

During this period, the typical symptoms of true comatose uremia were manifested. Nausea and vomiting, extreme weakness, restlessness and various psychic symptoms which progressed to apathy and coma, nosebleeds, marked anemia and nocturia were regularly noted. When ophthalmoscopic examination was performed, albuminuric neuroretinitis was found. The blood pressure rose to excessive heights, and marked retention of nitrogen rapidly developed. The specific gravity of the urine sank, and all tests showed severe impairment of renal function. In several instances, the blood chemistry was normal even two or three weeks before death. The amount of urea nitrogen would then rise to 40 or 50 mg per hundred cubic centimeters one week before death, and by the last day or two it might have risen to 130 mg per hundred cubic centimeters and even higher. So rapidly may this retention develop, that unless a chemical examination of the blood had been made just before death, it was found advisable to check it post mortem by determining the indican content of the blood. An indicanemia of 3 + or 4 + was considered adequate chemical evidence of uremia.²⁰

Gross Anatomic Observations—In most cases the gross observations at autopsy were typical of simple uremia. The characteristic observations that were accepted to establish the diagnosis of uremia were uredrosis, fibrinous pericarditis, hemorrhagic and ulcerative ileocolitis and petechial hemorrhages in the skin, the epicardium and the mucosa of the bladder. The heart was very large, far exceeding the normal

20 Monias, B. L., and Shapiro, P. The Value of the Indican Determination in the Blood in Cases of Renal Insufficiency, *Arch Int Med* 45:573 (April) 1930.

limits,²¹ with a firm, rubbery myocardium. The uremic picture was usually so brief that it was free from incidental noteworthy complications. In a few cases, however, hemorrhage from an acute peptic ulcer, uremic cerebral hemorrhage or focal bronchopneumonia had helped to terminate the case.

The kidneys were usually of almost normal size, each weighing about 120 Gm. The capsule was but slightly adherent. On separation, it left a diffuse, fine, evenly granular surface that was composed of small, irregular, purplish-brown elevations separated by narrow, deeper reddish-purple depressions. Bright red petechiae ranging in size from that of a pinhead to that of a millet seed were sprinkled over the surface. The hemorrhages were characteristic and served grossly to differentiate the kidneys from those in glomerulonephritis in which the hemorrhages are smaller and resemble "flea-bites." The cortex was not much reduced, being about 7 mm. in width. Surfaces made by section were light reddish-purple, mottled with lighter grayish-red areas. Cortical markings were obscure. Similar large petechiae were scattered over the sectioned surfaces and over the pelvic mucosa. The cross-sections of the arcuate arteries were thickened and gaping. The renal arteries were markedly thickened.

Microscopic Observations—Microscopic examination of the kidneys revealed that fully 60 per cent of the glomeruli were unchanged, about 10 or 15 per cent were completely or partly hyalinized, and about 10 per cent conformed to the ordinary type of hypertensive glomerulus, with decrease in size, apparent increase in the pericapsular connective tissue and simplification of tufts. From 15 to 20 per cent of the glomeruli, however, were enlarged to the size of a high power field and were fully rounded. Bowman's capsular epithelium was swollen, proliferated and sometimes thrown into a few layers. Bowman's spaces were usually narrow, but they often contained a little homogeneous, oxyphilic material with erythrocytes and a few leukocytes, and sometimes were filled with large or small hemorrhagic extravasations. The glomerular tufts were enlarged just as in a nephritis, but in marked contrast to nephritis, the individual capillary loops participated irregularly in the following changes. Sometimes only a few loops were involved and sometimes all of them. When the involvement was only partial, it was most frequently seen and was most severe near the hilus of the glomerulus.

The changes consisted of a swelling and desquamation of the endothelial cells, a swelling of the basement membrane and a swelling

21 Gewert, M. Ueber die Schwankungen des Herzgewichts in der verschiedenen Lebensaltern unter normalen und pathologischen Verhältnissen, Jena, Gustav Fischer, 1929.

and proliferation of the epithelial cells. Fine fat droplets were deposited abundantly in all elements of the thickened capillary walls. An occasional hyaline droplet was also noted. When the changes involved an entire glomerulus, it closely resembled the mild intracapillary glomerulo-

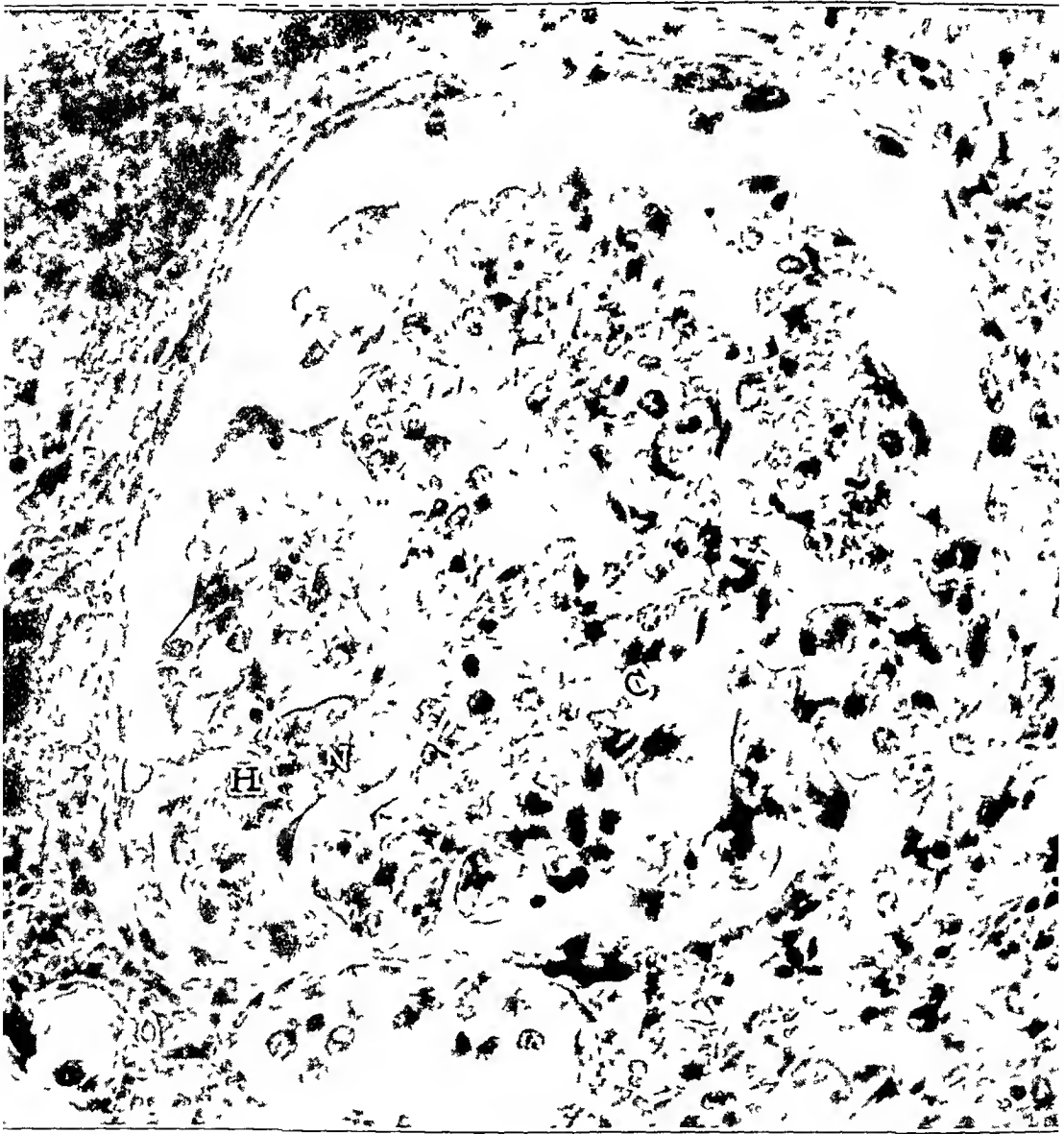


Fig 1—Prestatic glomerulus, with beginning necrosis. There are marked focal, capillary dilatation (*C*), slight proliferative and degenerative changes, and hyalinization of single capillary loops (*H*), and early necrosis (*N*). Note the hemorrhagic extravasation in the interstitial tissue. Leitz apochromatic 4 mm, periplanar 4, camera length 45 cm.

nephritis seen in older patients, as Klemperei and Otani pointed out. Usually, however, the changes involved only a few loops of one glomerulus and left the others unchanged. This focal character differ-

entiated it readily from nephritis in which every loop of every glomerulus is involved (Lohlein²²)

The same irregularity was noted in the blood content of the individual capillary loops. Some of the loops had apparently collapsed and were fused together. Some of them were widely dilated with erythrocytes and with a small but varying number of leukocytes and desquamated endothelial cells. In some glomeruli, all the capillaries were widely dilated, as if the whole glomerular capillary tuft had completely relaxed, in others, only a few capillaries were dilated. When the dilatation was focal, it was most frequently seen and most severe at the hilus of the glomerulus, this condition was associated with the most marked cellular changes previously described. The most common site of the worst dilatations as well as of the most severe cellular changes was the intraglomerular part of the afferent arteriole (fig 1)

In addition to these changes, there were certain other striking changes which affected but few of the enlarged glomeruli. In these glomeruli, single capillary loops, usually those most widely dilated and those near the hilus, showed a marked thickening and diffuse hyalinization of their walls, which in about 3 per cent of the glomeruli had advanced to an actual fibrinoid necrosis. In the hematoxylin and eosin sections, the necrotic capillary walls stained a smudgy purple, with fine deep blue granules of karyorrhectic nuclei, in contrast with the homogeneous, light pink cytoplasm and swollen, vesicular nuclei of simple hyalinization. Herxheimer²³ called attention to these differences, and demonstrated by Weigert's stain that this type of necrosis was actually associated with the appearance of a fibrinoid substance. Fat was demonstrated in abundant, irregular droplets in the necrotic walls.

Occasionally, the entire glomerulus was involved in the necrosis. Usually, however, there were only one or two necrotic loops near the hilus with numerous widely dilated, nonnecrotic loops at the periphery that showed only the proliferative, exudative and slight degenerative changes previously mentioned. The necrotic loops themselves sometimes appeared occluded, but they were usually the ones most severely dilated. When the necrosis involved many loops, there was sometimes an abundant infiltration of leukocytes, this was never seen when the necrosis was slight. In a few cases in which entire glomeruli were necrotic, fine granules of calcium were deposited, and the leukocytic reaction was marked. All of these changes were seen not only in the enlarged glomeruli, but also, occasionally, in the hypertensive glomeruli and even in the partly hyalinized ones.

22 Lohlein, M. Ueber die entzündlichen Veränderungen der Glomeruli menschlichen Nieren, Arb. a. d. path. Inst. zu Leipzig, 1908.

23 Herxheimer (footnote 12, second reference)

When necrosis affected a glomerulus, the intraglomerular part of the afferent arteriole was always severely involved. The extraglomerular part of the afferent arteriole also was practically always involved. But often the arteriole alone was necrotic, and either with a dilated lumen or even with an apparently obstructed lumen, led to a glomerulus that

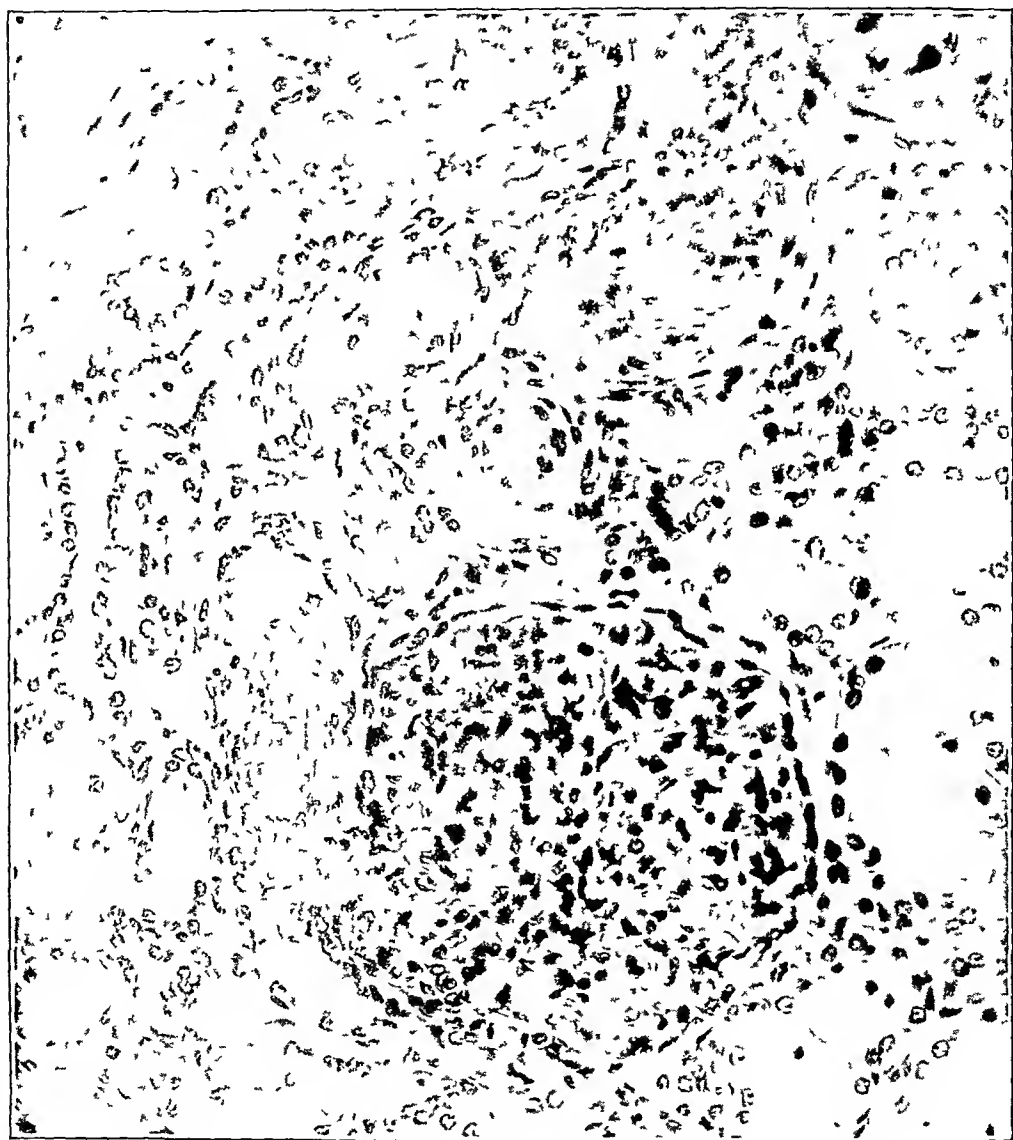


Fig 2—Necrotic arteriole winding toward its glomerulus, which shows no necrosis, but only the prenecrotic proliferative changes. Despite the apparent arteriolar occlusion, the glomerulus is still viable. Leitz apochromatic 16 mm, periplanar 4, camera length 45 cm.

showed no necrosis but only the proliferative and slight degenerative changes and the focal capillary dilatation previously mentioned (fig 2). In four cases only arteriolonecrosis was found in the kidney. The glomeruli presented all the other changes described, but no necrosis.

The arteriolar walls were thickened, they stained a smudgy purple, with fine, deep blue granules of nuclear disintegration, and they showed an extreme fatty degeneration. There was an indistinct limitation of the wall of the vessel and diffuse and localized aneurysmal dilatations. The

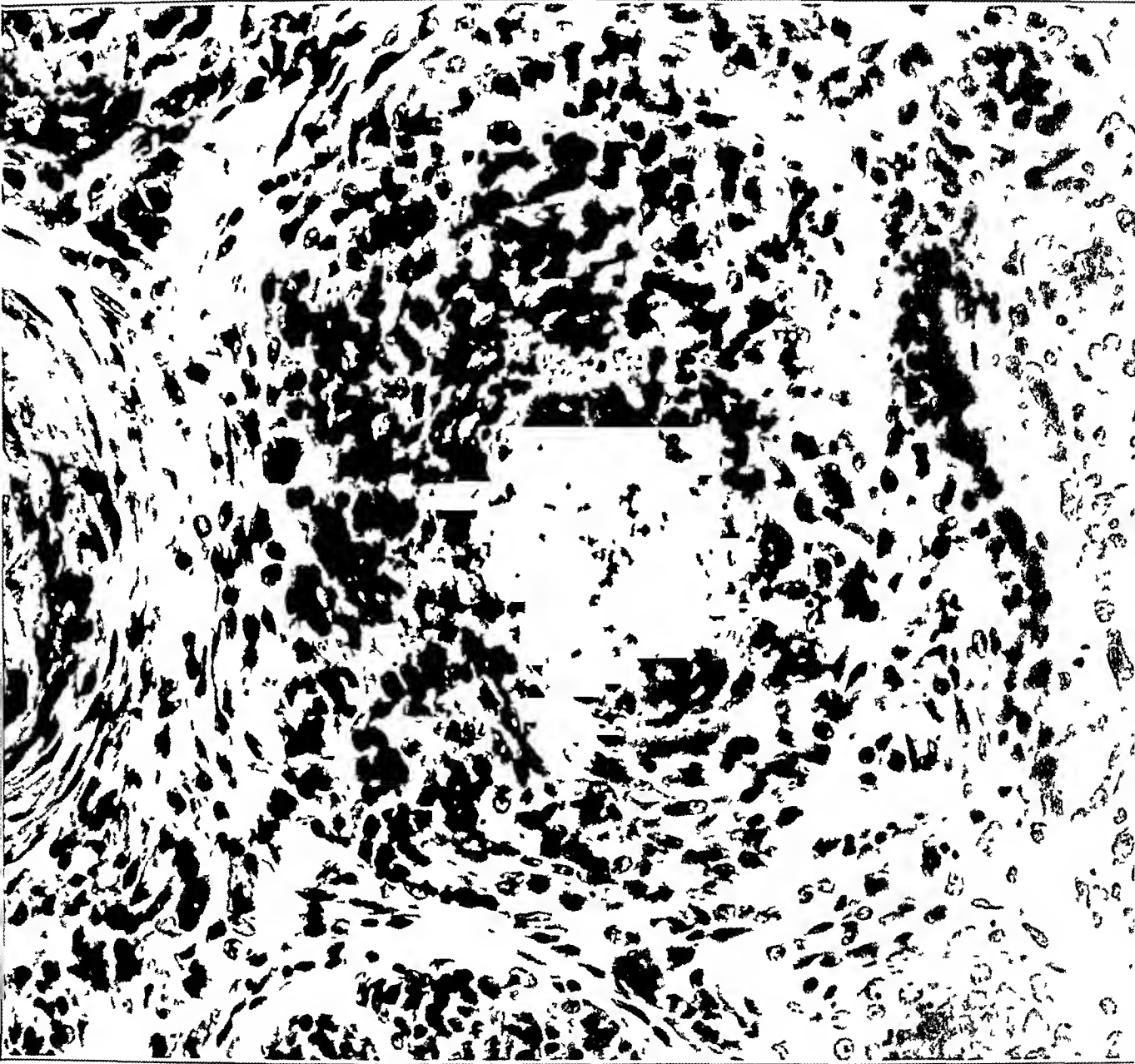


Fig 3—Necrotic arteriole. The arteriolar wall is impregnated by erythrocytes and leukocytes. It is surrounded by a periarteriolar nodule composed of proliferated adventitial cells and polymorphonuclear leukocytes. Leitz apochromatic 8 mm, periplanar 4, camera length 45 cm.

necrotic arteriolar walls were often impregnated by erythrocytes, and sometimes they were split by larger hemorrhagic extravasations, which extended widely into the adjacent interstitial tissue. This was the basis for the large petechial hemorrhages noted grossly. In places the arteri-

olar lumen was apparently obstructed, in other places it was only partly occluded by swollen endothelial cells, desquamated cells, erythrocytes, leukocytes and structureless debris

Occasionally, this fibrinoid necrosis extended proximally all the way to the intima of the small interlobular arteries. In a few cases such extensive necrosis was associated with the formation of periarteriolar nodules composed of swollen and proliferated adventitial cells with a few polymorphonuclear leukocytes (fig 3). In some cases, extensive necrosis was found without periarteriolar reaction, but the latter was found only intimately associated with severe necrosis. It was rarely present, but, when it appeared, it was directly proportional to the extensiveness of the necrosis. All transitions could be seen, from cases with moderately extensive necrosis and slight periarteriolar infiltration, to those with more extensive necrosis and the well defined picture of a periarteriolitis nodosa.

Necrosis usually involved only a small proportion of the arterioles. The remainder showed only an intimal thickening with hyaline and fatty degeneration. The large arteries, the arcuate arteries and the intertubular arteries showed a progressively more marked intimal thickening. In some branches, the thickened intima was dense, fibrotic and arranged in definite layers with elastica proliferation, as in the benign form of nephrosclerosis. This "hyperplastic intimal thickening" of Hueck²⁴ involved the arteries and arterioles that lead to the hypertensive and hyalinized glomeruli. In most of the vessels, however, the intimal thickening even exceeded that seen in benign nephrosclerosis, it was even more irregular and different in appearance. The intima was thick but loose, and was composed of a pale, light blue ground substance in which many star-shaped cells were loosely suspended, and in which but few collagenous and elastic fibrils were loosely scattered. The picture corresponded to the "regenerative intimal thickening" of Jores, which Hueck clearly outlined as being only a more rapidly developing form of hyperplastic intimal thickening. These vessels were associated with the enlarged necrotic or pre-necrotic glomeruli described. Fine fat and hyaline droplets were deposited in the deeper layers of the thickened intima. The media was usually atrophic, but occasionally it showed an apparent slight hypertrophy.

The convoluted tubuli showed a striking degeneration of the hyaline droplets. This degeneration was practically never seen in the benign form. Many of the tubuli were filled with extravasated erythrocytes. The interstitial tissue was slightly increased focally, within it, the

24 Hueck, W. Ueber das Mesenchym, Beitr z path Anat u z allg Path 66 330 1920, Anatomisches zur Frage nach Wesen und Ursache der Arteriosklerose, Munchen med Wchnschr 67 535, 1920

pericapsular branch of the afferent arterioles was sometimes seen to be dilated but the efferent arterioles and the intertubular capillaries were not dilated as in cases of passive congestion.

In other organs arteriosclerosis and arteriolosclerosis were less constantly seen. In the spleen they were common, but in this organ



Fig 4—Pronecrotic glomerulus in the periphery of a miliary tubercle. Note the Langan's giant cells at the left hand edge. These were in the periphery of the tubercle. Note the hemorrhagic extravasation in Bowman's space of the glomerulus. Litz apochromatic 8 mm, periplanar 4, camera length 45 cm

they are physiologic in old age. These conditions were found often in the pancreas and liver and occasionally in the suprarenal gland. Necrosis was never seen outside the kidneys, except in one case in which the spleen showed multiple areas of necrosis. The "speckled spleen"

reported by Feitis²⁵ had been reported only in cases of nephrosclerosis with uremia. Necrosis of the pancreas has also occasionally been reported by others.⁵

In two cases, the malignant renal changes were accompanied by other complicating renal conditions. In one case (case 22) in which there was generalized disseminated miliary tuberculosis, there were numerous miliary tubercles in the previously sclerotic kidneys. In the epitheloid zone of these tubercles and even beyond them, necrotic and pre-necrotic glomeruli and necrotic arterioles were found (fig 4). In case 23, pyelonephritis was similarly associated.

In the remaining eight cases (cases 24 to 31), there was a discrepancy in the histologic observations. The clinical picture conformed exactly with that of classic malignant nephrosclerosis. The general observations at autopsy were the same, except that there was usually some severe complication that had hastened the fatal termination. The kidneys were grossly identical, except that the petechial hemorrhages were scanty or absent. Microscopic examination revealed most of the changes already described with an even more widespread and more marked focal and glomerular capillary dilatation, with enlarged glomeruli, proliferative and degenerative changes and intimal thickenings. In some of the enlarged glomeruli, with markedly dilated capillary loops, some of the loops near the hilus showed a marked, hyaline thickening. Actual necrosis of glomeruli or arterioles could nowhere be found. In seven of these cases, the only suggestion of early necrosis was a slight smudgy purple transformation of the hyalinized capillary loops that have been described. In case 30, a marked preceding sclerotic parenchymal atrophy was also present, this atrophy had probably contributed to the renal failure.

Among the 1,000 cases in which autopsy was performed there were 42 of glomerulonephritis. Twenty-four of the patients had died in uremia, and 18 through some factor other than uremia. In the uremic group there were 4 cases of chronic nephritis and 1 of subacute nephritis which showed the same type of glomerulonecrosis and arteriolonecrosis. One case of chronic and one of subacute nephritis showed only arteriolonecrosis (table 2). In one case of rapidly progressive subacute nephritis in a child 12 years of age, there was an extensive glomerulonecrosis and arteriolonecrosis as it is seen in the most severe cases of malignant nephrosclerosis, accompanied by periarteriolitis nodosa. One case of chronic nephritis showed a focal capillary dilatation with but slight necrosis. Four cases showed the glomerular capillary dilatation with no

25 Feitis, H. Ueber multiple Nekrosen in der Milz, Beitr. z. path. Anat. u. z. allg. Path. 68: 297, 1921.

TABLE 2—*Glomerulonephritis with Prestasis or Necrosis*

Post mortem No	Color	Sex	Age	Signs of Uremia	Weight of Kidneys, Gm	Weight of Heart, Gm	Symphylitic Aortitis	Contributory Cause of Death	Clinical Impression	Duration 1 mos	Blood Chemistry	Blood Pressure 210/116	Kahn Test	Histologic Observations
1	149	C	M	34	+	320	560	—	Chronic nephritis	1 yr	Urea nitrogen 135, creatinine 11	300/156	—	Necrosis, chronic nephritis
2	219	C	F	50	+	200	500	—	Chronic nephritis	1 yr	Urea nitrogen 106	191/110	—	Chronic nephritis, necrosis
3	334	C	F	43	+	315	697	+	Uremia	8 mos	Urea nitrogen 93, creatinine 6	224/154	—	Necrosis, chronic nephritis
4	791	W	F	43	+	300	495	—	Chronic nephritis	5 wks	Urea nitrogen 60, creatinine 16	251/150	—	Necrosis, chronic nephritis
5	185 (1930)	C	F	29	+	315	350	—	Uremia	6 wks	Urea nitrogen 82, creatinine 5	140/90	—	Necrosis, subacute nephritis
6	113	W	F	12	+	300	260	—	Chronic nephritis	3 mos	Urea nitrogen 124, creatinine 9	275/160	—	Necrosis, perivascularitis, subacute nephritis
7	185 (1929)	C	M	35	+	223	640	+	Acute nephritis	3 wks	Urea nitrogen 142	210/150	—	Necrosis, arteriolar phritis, subacute nephritis
8	704	C	M	38	+	310	720	—	Uremia	3 mos	Urea nitrogen 139, creatinine 13	210/150	—	Prestasis, no necrosis, chronic nephritis
9	200	C	M	10	+	275	500	—	Uremia	9 days	Urea nitrogen 126, creatinine 12	190/150	—	Prestasis, no necrosis, acute nephritis
10	137	C	F	40	+	275	500	—	Uremia	5 mos	Urea nitrogen 148, creatinine 12	115/85	—	Prestasis, no necrosis, chronic nephritis
11	614	W	M	22	+	500	375	—	Uremia	9 days	Urea nitrogen 70, creatinine 7	250/145	—	Prestasis, no necrosis, chronic nephritis
12	61	C	F	40	+	200	455	—	Uremia	5 mos	Urea nitrogen 148, creatinine 12	115/85	—	Prestasis, no necrosis, chronic nephritis

suggestion of necrosis. One case had progressed to uremia through advanced parenchymal atrophy. The rest showed no marked atrophy or necrosis and only an occasional dilated capillary loop. The hyaline drop degeneration of the convoluted tubuli was as striking as in the cases of malignant nephrosclerosis.

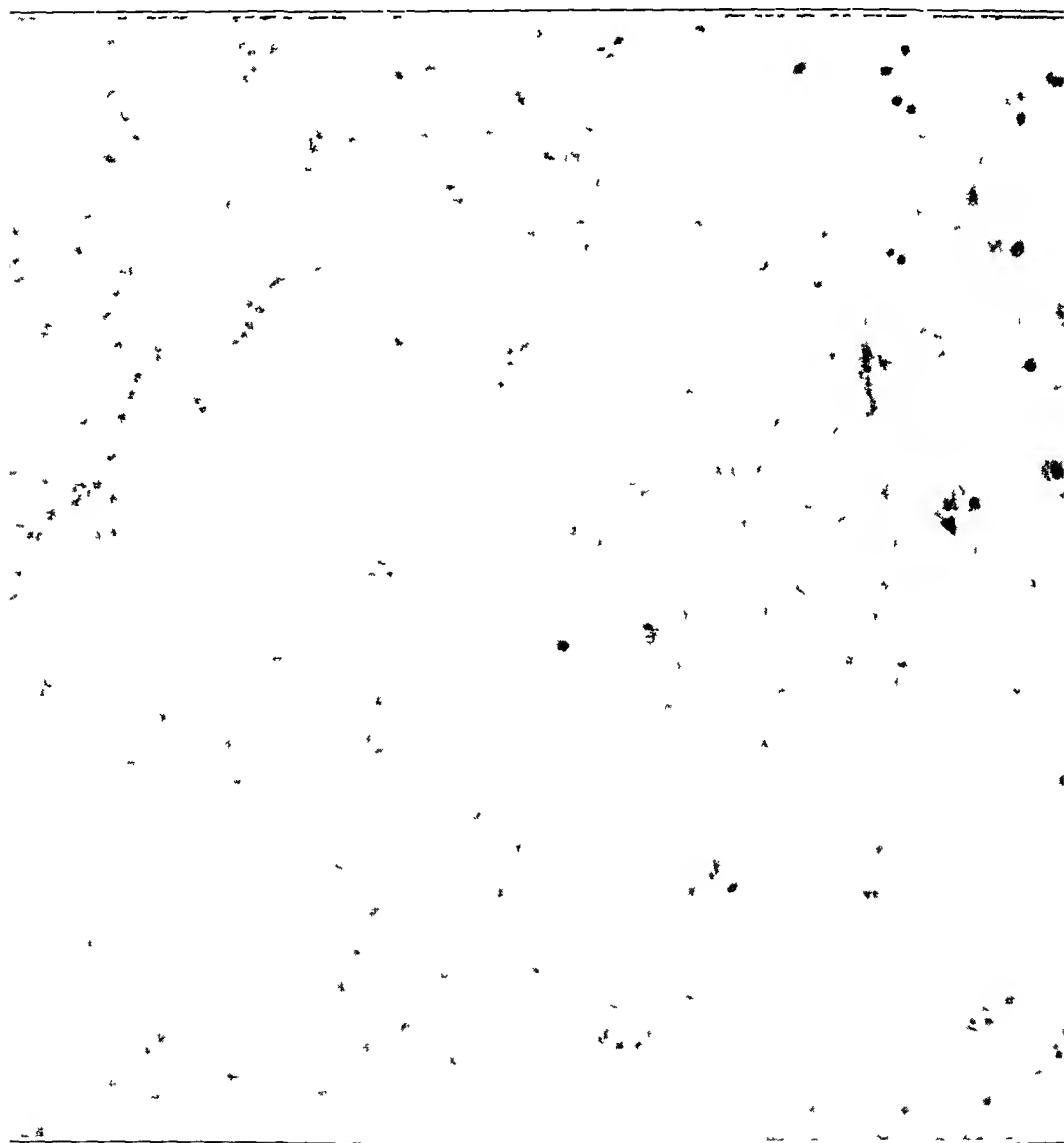


Fig 5—Hyaline necrosis in anemic center of an infarct. Leitz apochromatic 4 mm, periplanar 4, camera length 45 cm.

Necrosis of the glomeruli or the arterioles was never seen in any of the cases of benign nephrosclerosis. However, occasional observations of this kind have been reported by others, even by Fahr. The other changes, however, were seen more frequently. In case of benign nephrosclerosis that terminated through some factor other than uremia, an occasional enlarged glomerulus with slight proliferative and degenera-

tive changes could be found. Even more commonly, an irregular, focal, glomerular capillary dilatation similar to but not as marked as that seen in the malignant form was noted. Here, too, it was most common and severe near the hilus of the glomerulus, and in the intraglomerular part of the afferent arteriole.²⁶ The eight cases of malignant nephrosclerosis

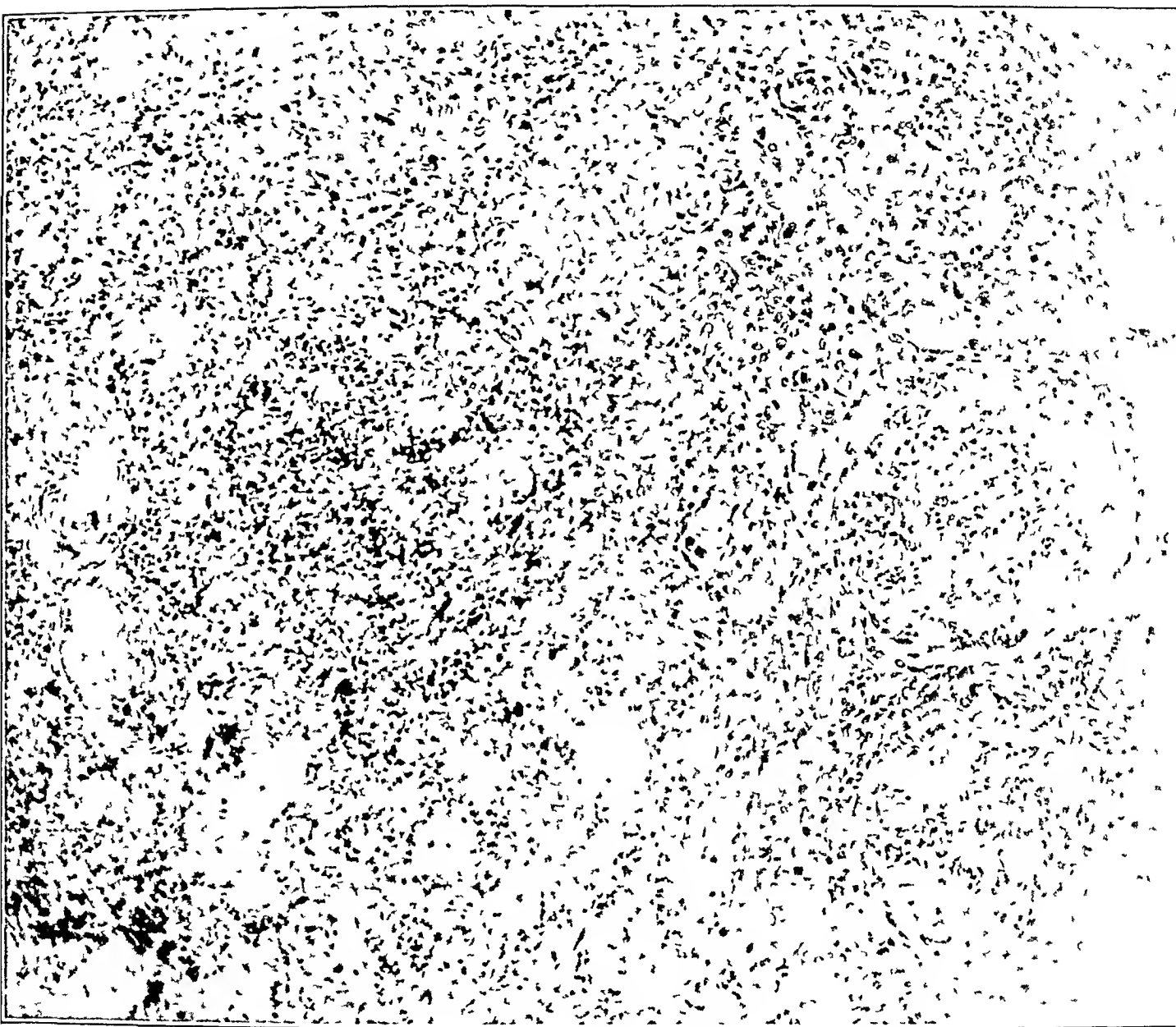


Fig 6—Fibrinoid necrosis in hyperemic periphery of the same infarct. Lertz apochromatic 16 mm, periplanar 4, camera length 45 cm

without necrosis but with marked capillary dilatations, proliferative and preneurotic changes presented all transitions between the cases of benign nephrosclerosis without necrosis and the cases of malignant nephro-

²⁶ Jaffe, R. H. The Vascular Changes of the Kidney in Hypertension, *Am J M Sc* 169 88, 1925

sclerosis with necrosis. These transitions without necrosis but with vascular dilatations strengthened the impression that benign and malignant nephrosclerosis were essentially the same, differing only in the speed of development. The feature common to all cases was the presence of irregular, focal, capillary dilatations.

The marked capillary dilatations seen in the malignant and in the transition forms and the less marked dilatations seen in the benign forms suggested, however, that something was wrong with the ischemic hypothesis. Ischemia, also, was not compatible with the proliferative changes observed. Proliferation requires an increased and not a decreased amount of nutrient fluid. Indeed, the proliferative and pre-necrotic changes were found intimately associated with the most widely dilated capillaries, and not with the ischemic ones. Volhard held that the proliferative changes were reactions to ischemic degeneration, but they were often marked when there was little or no degeneration with them. Furthermore, ischemia does not produce a fibrinoid type of necrosis, but a hyaline necrosis. The swollen, oxyphilic, hyaline ghosts of glomeruli in the bloodless centers of anemic infarcts (fig 5) are altogether different from the proliferated, degenerated and necrotic glomeruli, identical with those of malignant nephrosclerosis seen in the periphery of the infarcts (fig 6). The glomeruli are found only in the periphery of the recent infarcts, in the zones of hyperemia and leukocytic infiltration and marked circulatory disturbances, but never in the anemic centers. Therefore, to secure a more reliable impression of the actual state of hyperemia or ischemia in the renal blood vessels of malignant nephrosclerosis, a series of injection experiments was performed.

EXPERIMENTAL INJECTION

Renal injections have been applied many times before. All writers have concurred that in nephrosclerosis renal permeability is markedly reduced. Rigo²⁷ perfused normal and pathologic kidneys with horse serum at body temperature and at constant pressures. He found that normally, from 90 to 200 cc of serum would pass through the vessels of the kidney within five minutes. In sclerotic kidneys, the perfusibility was so markedly reduced that only from 4.5 to 8 cc would get through within this time.

Doenecke and Rothschild²⁸ perfused kidneys with physiologic solution of sodium chloride at body temperature, but at varying pressures.

27 Rigo A. Untersuchungen über die postmortale Durchstromungskapazität des Nierenblutgefäß-Systems bei verschiedenen Erkrankungen, Frankfurt Ztschr f Path **31** 1, 1925.

28 Doenecke, F, and Rothschild P. Ueber das Verhalten der postmortalen Durchstromungskapazität des Blutgefäß-Systems der Niere bei Erkrankungen mit und ohne Blutdrucksteigerung. Zentralbl f inn Med **48** 866, 1927.

With normal kidneys, perfusion began at from 10 to 50 mm of mercury and at 120 mm amounted to 100 cc per minute. With sclerotic kidneys perfusion did not begin until a pressure of at least from 80 to 150 mm of mercury was used. At 150 mm, the salt solution might barely squeeze through, and at 200 mm of mercury, the perfusion would amount to only 4 cc or so, per minute.

Baehr and Ritter¹⁹ reviewed the various methods of injection used. They injected barium sulphate-gelatin mixtures into kidneys and then visualized the injection by x-rays. They were able to demonstrate in the x-ray pictures of sclerotic kidneys a marked reduction in vasculature. They emphasized the circulatory embarrassment as the mechanism of renal insufficiency.

Hayman²¹ has done the most recent and accurately quantitative work in this field. He measured the outflow from the renal vein during perfusion at various pressures and correlated this with roentgenograms of the vessels taken after injection and with histologic study. His conclusions were the same. For example, he found that the perfusibility of normal kidneys at 100 mm of mercury was 1.7 cc per gram per minute. In sclerotic kidneys, the perfusibility at 100 mm was 0, and at 200 mm it had reached only 1 cc per gram per minute.

The method used here was somewhat similar to that of Hayman. Kidneys were removed at autopsy and perfused as soon as possible, usually within an hour or two. The left kidney was usually used and the right kidney was taken for the immediate gross and histologic examination necessary to establish the diagnosis. The renal artery and vein were left as long as possible. The entire kidney, embedded in its pararenal fat, together with its suprarenal gland, was tied off and removed.

The artery and the vein were cannulated. The kidney was first perfused with 2 liters of physiologic solution of sodium chloride, at 37 C, until it was washed uniformly white. An ordinary clinical baumanometer was inserted in the circuit, and the perfusion was conducted at whatever systolic blood pressure was recorded for the patient. The numerous small leaks from the small vessels of the pararenal fat tissue and especially of the renal hilus were carefully tied off.

During this preliminary washing the observations of Hayman and of Doenecke were readily repeated. Perfusion through normal kidneys occurred freely. At pressures of 100 mm of mercury, the salt solution issued in full stream from the renal vein. With the sclerotic kidneys, even at 200 and 240 mm of mercury, the salt solution trickled through, only drop by drop, with the greatest difficulty. If the pressure

²⁹ Hayman, J. M. Experiments on the Patency of the Blood Vessels of Nephritic Kidneys, *J. Clin. Investigation* 8:89, 1930.

used for perfusion was allowed to fall to 180 or 160 mm, no fluid would pass through the kidneys

When the renal vessels had been washed as clean as practicable with salt solution, an india ink solution was used for perfusion. Here the difficulty in perfusion was even more apparent than with the salt solution. The india ink flowed easily through normal kidneys, but squeezed through the sclerotic kidneys very slowly, even at high pressures. This was attributed to the somewhat greater viscosity of the ink solution. The viscosity of the ink as determined by the Hess capillary viscosimeter was 120. That of blood serum was 125. Dilution of the ink with 0.9 per cent salt solution or with 6 per cent acacia in 0.9 per cent salt solution reduced the viscosity, but gave no better end-results. Even at a dilution of 1:8, with a viscosity of 87.5, but little more ink came through. Accordingly, the conclusion was drawn that the primary vascular impairment of permeability was already so great that the differences in the viscosity of the perfusion fluid became an insignificant factor.

The perfusion with ink was maintained for about one hour. The kidneys were then fixed at once in a diluted solution of formaldehyde, U. S. P. (1:10). A small piece was also fixed in alcohol. Frozen and paraffin sections were then made of the kidney into which ink had been injected; they were stained with hematoxylin and eosin and with sudan III, and compared with the uninjected kidney of the same patient. No appreciable difference in result was obtained between the material fixed in formaldehyde and that fixed in alcohol, between the frozen sections and the paraffin sections or between the perfusions with low dilutions of india ink and those with high dilutions.

Examination of all of these sections revealed that in normal kidneys the ink was present in a large majority of the glomeruli. In the sclerotic kidneys, it was present in but a part of the glomeruli with the surprising feature that the injection of ink had particularly favored the glomeruli that were most severely involved in the malignant changes. In a given section, with 60 per cent or more of the glomeruli unchanged, few of the normal glomeruli contained ink. Of the 20 per cent or so of partly hyalinized or hypertensive glomeruli, a somewhat larger number contained ink, and these were usually the ones with the early malignant changes. The enlarged glomeruli, numbering only 15 or 20 per cent of the total, presented the greatest actual number of injected ones. The more severely damaged the glomerulus, the greater was the amount of ink that had accumulated within it (fig. 7).

Not only did the ink favor the pathologic glomeruli over their more numerous, normal neighbors, but in a single glomerulus, the ink was most abundant at the site of the most severe changes. If only a few capillary loops were involved in proliferation and focal dilatation, the ink appeared only in those loops. If only one or two loops near

the hilus were necrotic, the ink was found within these necrotic loops, and less abundantly or not at all, in the less severely involved, more peripheral ones (fig 8)

With the injection of ink it was found that the arterioles that were apparently occluded in the uninjected specimens possessed widely filled

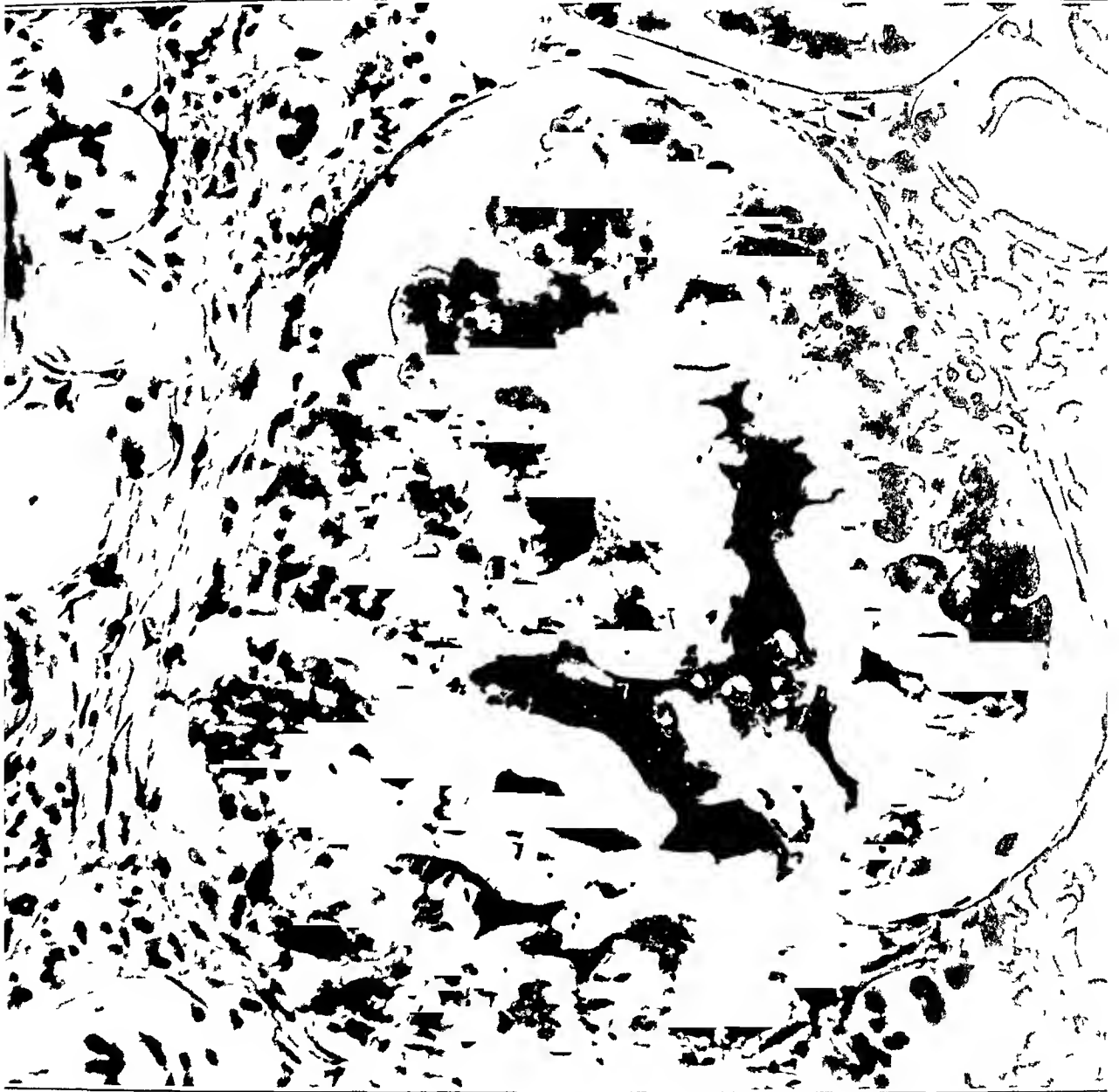


Fig 7—Prenecrotic glomerulus injected with india ink. Note the severe capillary dilatations, approaching an almost complete relaxation. Leitz apochromatic 4 mm, periplanar 4, camera length 45 cm.

lumina. Necrotic arterioles with dilated lumina filled by ink led freely into their corresponding necrotic or prenecrotic glomeruli. Adjacent normal or hyalinized arterioles with their normal, hypertensive or hyalinized glomeruli were more often empty of ink.

So far it was apparent that the more severe the glomerular changes, the greater was the amount of blood contained in the involved capillary loops. This was checked by the injection of ink which had accumulated most abundantly in the loops that were most severely damaged. It could therefore be concluded that hyperemia, not ischemia, was associated with

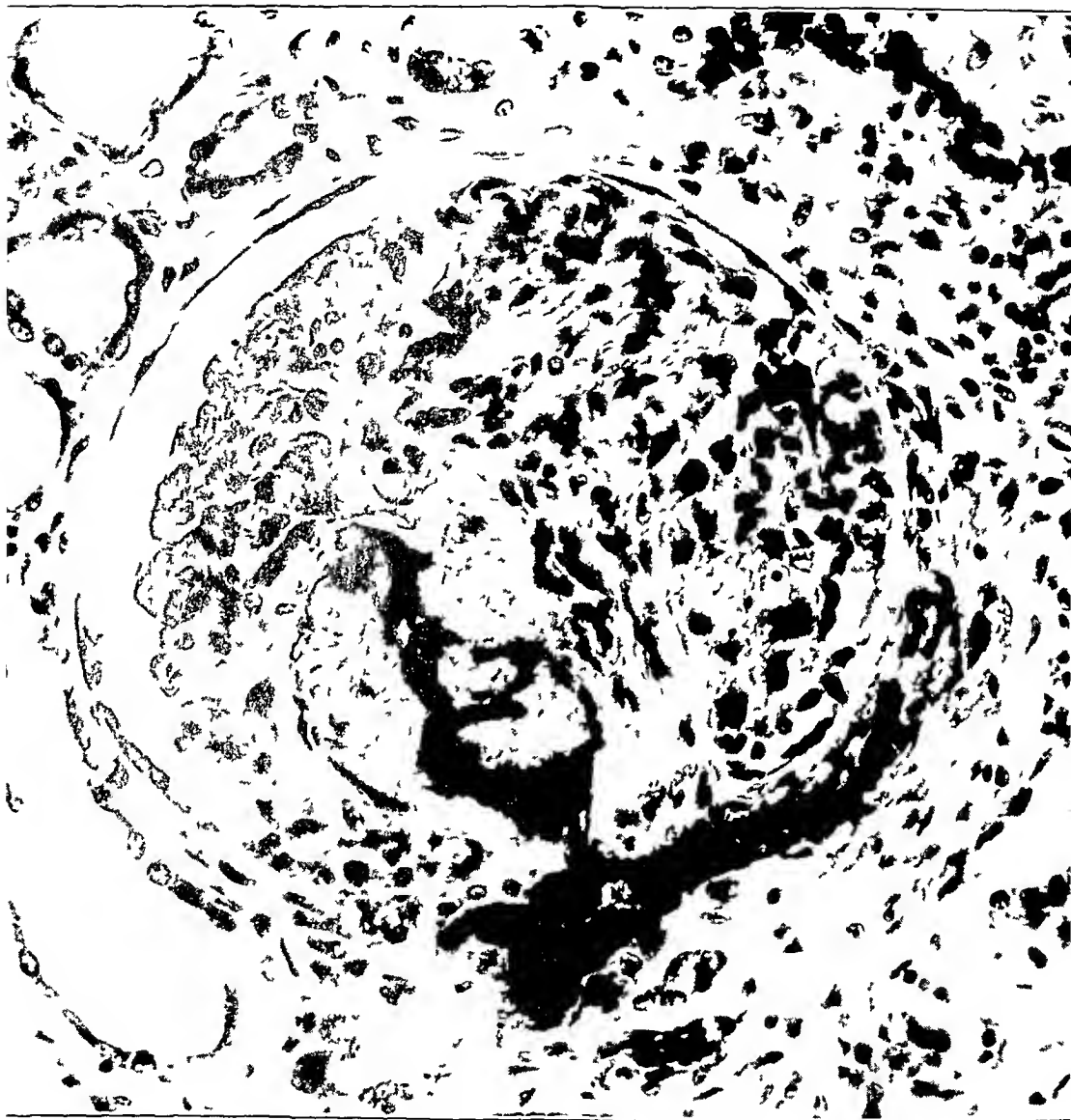


Fig 8—Necrotic glomerulus injected with india ink. The ink is seen just within the capillary loop that is most extensively necrotic. It is seen also in the dilated afferent arteriole and in the pericapsular branch of the afferent arteriole, but it had not reached the efferent arteriole or the intertubular capillaries. Lutz apochromatic 8 mm, periplanar 4, camera length 45 cm.

these malignant changes. Klemperer and Otani had already noted the vascular dilatations in malignant nephrosclerosis, but had explained them on the basis of back flow from adjacent normal glomeruli, through the efferent arterioles.

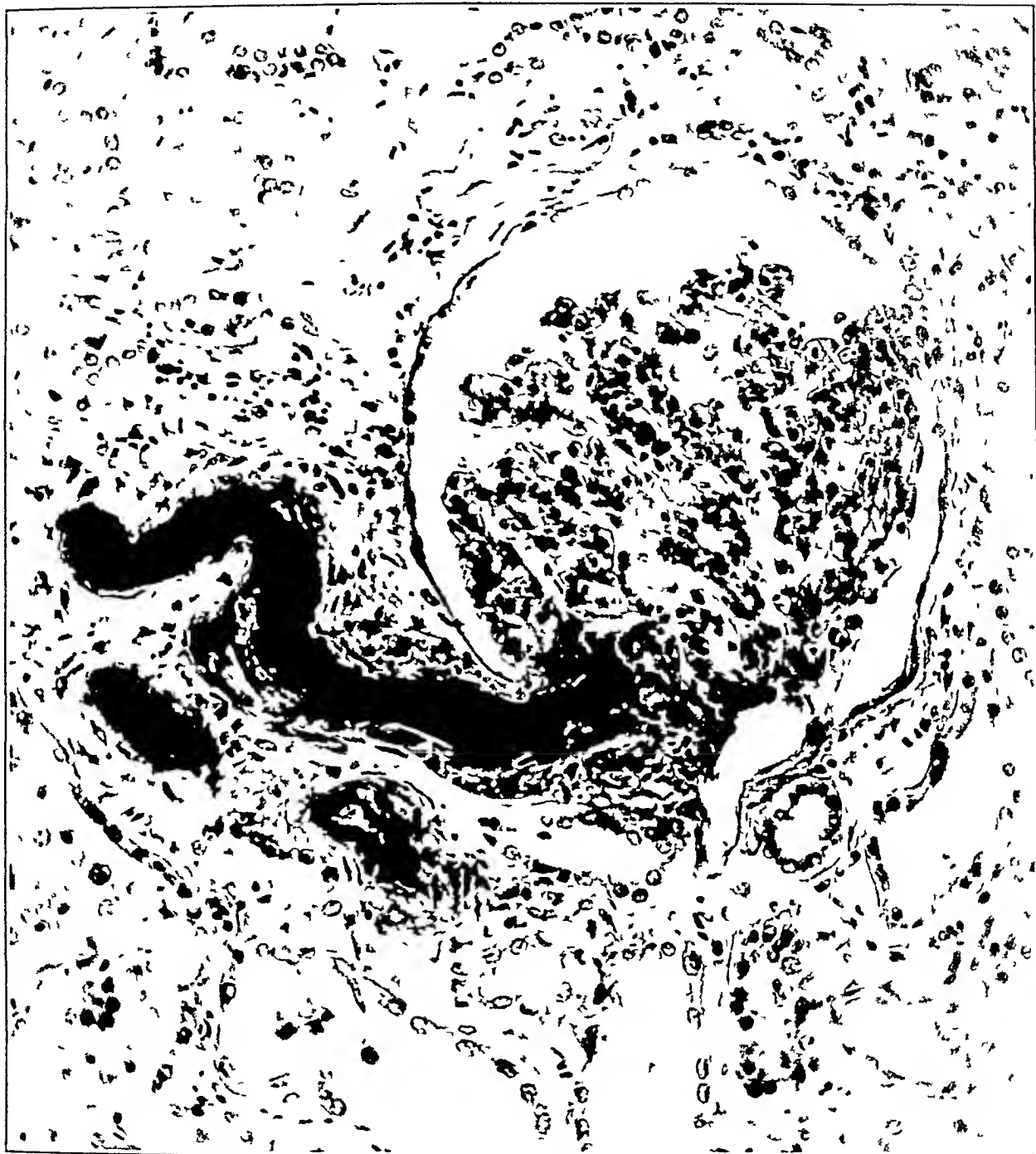


Fig 9—Specimen from serial sections in which the injection of ink could be followed from the interlobular artery directly through the necrotic, dilated, afferent arteriole into the pre-necrotic glomerulus. Leitz apochromatic 8 mm, periplanar 4, camera length 45 cm.

Since with all the difficulty of injection, ink was found most abundantly in the necrotic glomeruli, it is unlikely that it could have reached them by back flow from their normal neighbors. That this hyperemia was not a result of back flow was further indicated by the fact that the ink was found more abundantly at the hilus of the involved glomeruli than at the periphery, and finally by the fact that little or no ink was found in the efferent arterioles or intervening intertubular capillaries.

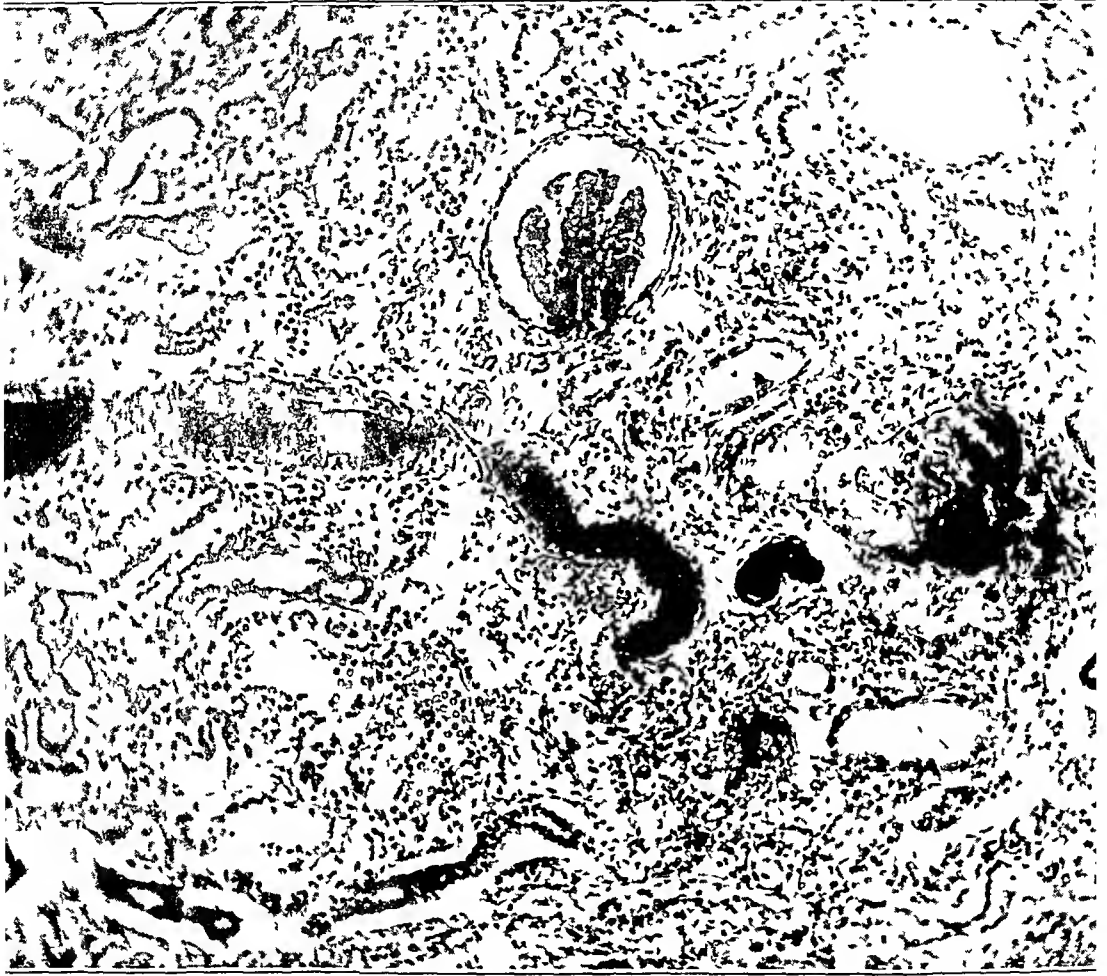


Fig. 10—Specimen from serial sections in which the injection of ink could be followed from the interlobular artery directly through the necrotic, dilated, afferent arteriole into a diffusely necrotic glomerulus. An adjacent normal glomerulus is uninjected. Leitz apochromatic 16 mm, periplanar 4, camera length 45 cm.

To confirm this point, however, serial sections were made from the specimens into which injections had been made. In these sections, the injected ink could be followed clearly from the intertubular artery directly through the necrotic afferent arteriole into the necrotic (fig. 10) or pre-necrotic (fig. 9) hyperemic glomeruli. Occasionally it was traced into the pericapsular branch of the afferent arteriole (fig. 8), but it

never originated in the efferent arterioles or intertubular capillaries. The hyperemia was therefore conclusively direct and not retrograde.

COMMENT

It was difficult to reconcile these observations. Nephrosclerosis is undeniably associated with ischemia. Even the experiments described showed the extreme slowness and difficulty with which blood passes through these kidneys at even very high pressures. Also the impaired permeability during life is almost certainly the basis for the renal functional insufficiency. Ischemia exists and may well be accepted as the cause of the uremia. But ischemia as such is not the basis for the characteristic pathologic changes. These changes were intimately and proportionately associated, not with ischemia, but with a direct hyperemia.

The confusion arose from failure to recognize that vascular dilatation does not necessarily denote hyperemia. It is an example of the failure of morphologic investigation when unsupported by physiologic correlation. What really existed was a hyperemia in the sense that a given portion of the vascular tree at any one time contained a greater quantity of blood but an ischemia in the sense that the blood was passing through these vessels much more slowly than before. What really occurred was a hyperemia with retardation, just as it is seen in any inflammatory lesion (Fahraeus³⁰). The retardation may proceed to complete stasis. For the less severe degrees of this condition, Jaffe suggested the term "priestasis." The vessels are widely dilated, the blood is flowing through them very slowly or not at all.

Gustav Rickes¹⁷ first propounded this conception to explain the paradox that I encountered of hyperemia associated with ischemia. He based his conclusions on direct studies on the living animal and on occasional observations on human beings during surgical operation. According to his views, the arteries, arterioles and capillaries are innervated organs, with a double nerve supply regulating constriction and dilatation. Moderate stimuli produce moderate contraction, strong stimuli produced marked contraction, excessive stimuli produce a loss of constrictor tonus, with paralysis. Dilator tonus is less sensitive and is retained after constrictor tonus is lost. Excessive stimuli, therefore, result quickly, not in contraction, but in dilatation.

The arterial tree reacts segmentally. Its peripheral portions are progressively more sensitive than the proximal portions. A stimulus that is sufficiently strong to cause marked contraction of a larger artery constitutes an excessive stimulus for the capillaries and arterioles and

³⁰ Fahraeus, R. The Suspension Stability of the Blood, *Physiol. Rev.* **9**: 241, 1929.

results in their dilatation. This dissociation in reaction between arterial contraction and peripheral dilatation is not always uniform. But whenever and wherever it occurs, there is a marked decrease in the velocity of flow through the involved, dilated, peripheral bed. The narrowed arterial stream is retarded as it enters the dilated arteriole and capillary, just as the current of a river slows down when it empties into a lake. The greater the peripheral dilatation, the greater will be this retardation.

This dissociation in reaction is the normal vascular neurogenic mechanism by which the vessels of an organ regulate the total blood supply, and by which the blood supply to the various functional units is constantly being shifted and changed. These rapid vascular changes play a particularly prominent rôle in the kidney, in which rapid functional changes are constantly going on, as part of the mechanism to insure physiologic hemostasis of the organism (Cannon³¹).

Only on exaggeration of this normal, neurogenic, vascular mechanism do organic pathologic changes follow. The nutrition of the vascular walls and of the adjacent tissues depends on the speed with which blood is flowing through their lumina and partly also on the adventitial supply which is being similarly regulated. Constriction of the artery gives a more rapid flow of blood and with it a faster interchange of nutrient fluids between the lumen and the wall. With dilatation, the blood stream is retarded, and two changes follow: (1) a liquor diapedesis, an imbibition of the walls with an increased amount of nutrient fluid, and (2) a decrease in rate of interchange of nutrient fluids between the lumen and the wall. The increased amount of imbibition of fluid favors cellular proliferation and swelling. The decreased rate of the interchange of fluid favors degenerative changes. These two factors vary in the importance of their effect with the degree of dilatation and slowing.

If the peripheral dilatation is moderate, there is moderate retardation and a moderately increased amount of imbibition of fluid within the vascular walls. This is adequate for only a limited cellular proliferation within the somewhat thickened vascular walls, but a more marked elastic and collagenous fibrillar differentiation slowly takes place. The decreased rate of interchange of fluid favors the slow deposit of elastin and collagen and, finally, of a small amount of hyalin and fat. The prolonged retardation finally ends in slow atrophic changes.

If retardation is marked, there is a marked imbibition of the walls of the vessels with nutrient fluid. They rapidly become much swollen. The markedly increased amount of nutrient fluid within them determines an active proliferation of the young, star-shaped, mesenchymal

31 Cannon, W. B. Organization for Physiological Homeostasis, *Physiol. Rev.* 9: 399, 1929.

cells, while as yet only a few scattered fibrils have had time to differentiate. Fat is abundantly deposited because of the factor of decreased rate of interchange of fluid.

Severe dilation brings with it a severe retardation of flow. There is an even more marked imbibition of fluids, so that the vessels become much swollen with it. But the decrease in rate of interchange of fluid is now so great that even the increased amount of nutrient fluid rests sluggishly within the swollen walls of the vessels. It is valueless for cellular proliferation, and only a marked fatty and hyaline degeneration occurs. Finally, with extreme dilatation there is almost complete stasis of flow. The walls of the vessels swell up with fluid, but the extreme retardation of interchange of nutrient fluid establishes a complete cessation of the nutrient supply to the vascular wall. The viability of the vascular wall is imperiled, and as fibrin is deposited from the imbibed fluid a fibrinoid necrosis finally results.

As the stream slows down, not only liquor diapedesis, but erythrodiapedesis takes place, red blood cells and even leukocytes filter out of the dilated lumen through the walls of the vessels into the tissue spaces (see Fahraeus ³⁰). Even before necrosis takes place, this erythrodiapedesis in the glomeruli and arterioles may thus result in moderate hematuria and small petechiae in the kidney. When necrosis finally occurs, the walls of the dead vessels given way under any returning pressure of blood, dilate and break, so that the larger, petechial, hemorrhagic extravasations of malignant nephrosclerosis are formed. If the patient still lives, leukocytes accumulate about the necrotic walls of the vessels, and even calcium salts may be deposited from the blood stream in the partly necrotic tissues. With prestasis sufficiently severe to cause an extensive arteriolar necrosis, there is a similar circulatory and nutritional disturbance in the periaarteriolar tissue. The adventitial cells proliferate in response to the imbibition of fluid, and with the leukocytes which accumulate about the walls of the necrotic vessels, form periaarteriolar nodules. The periaarteriolitis is thus only a later stage of extensive necrosis. Ricker similarly accounted for the changes of periaarteritis nodosa on a similar vascular and periaarterial, prestatic mechanism (Ricker ¹⁷ and Gruber ³²).

All of the pathologic changes that appear in benign and malignant nephrosclerosis may thus be accounted for on the basis of various degrees of the mechanism of retardation. In benign nephrosclerosis, the dissociation in reaction between arterial contraction and peripheral dilatation is moderate. The retardation, the nutritional impairment and the consequent changes are slight, drawn out over a long period, they

³² Gruber, G. B. Periaarteritis nodosa, *Virchows Arch f path Anat* **258** 441, 1925

slowly induce a hyperplastic intimal thickening of the arteries and arterioles and a gradual hyalinization and atrophy of the glomeruli. In malignant nephrosclerosis, the dissociation is marked and the dilatations are extreme, finally the retardation approaches almost complete stasis. The nutrient supply is markedly reduced in the dilated vessels, and severe changes rapidly result. There is at first a loose intimal swelling with cellular proliferation from the factor of increased amount of imbibition of fluid. As complete stasis is approached, the factor of decreased rate of interchange of fluid predominates, proliferation stops and severe fatty and hyaline degeneration and finally fibrinoid necrosis result.

Exactly the same mechanism is responsible for the changes seen in nephritis, in periarteritis nodosa or in inflammations anywhere in the body. Ricker pointed out that the ischemia of nephritis is a postmortem illusion, brought about by agonal vascular emptying in the hypertonic organ. When accidentally observed during life, nephritic kidneys are hyperemic. When biopsies are taken from them, they bleed much more furiously than do normal kidneys. What actually occurs in nephritis is a retardation hyperemia. The proliferative, exudative, degenerative and even necrotic changes that are seen are based on the same mechanism as that in benign or malignant nephrosclerosis, except that it is more diffuse. In nephritis, the vascular dissociations involve uniformly every capillary loop of every glomerulus.

The resemblance of malignant nephrosclerosis to nephritis, as well as its resemblance to benign nephrosclerosis and the occasional transition between them all is therefore not surprising. All these pathologic processes are based, not on ischemia as such, but on the same mechanism of retardation hyperemia resulting from excessive dissociation between arterial contraction and peripheral dilatation. In nephritis the process is moderate. The proliferative, exudative and slight degenerative changes of moderate retardation predominate. But the process is so diffuse that though it is moderate in degree, the entire kidney is at once thrown out of function, and uremia quickly develops. The necrosis of severe prestasis is infrequently seen and then only in the violent cases with "sturmischen Verlauf" (stormy course), or in older patients with a predisposing arteriosclerosis.

In benign nephrosclerosis, the process is moderate. It is also not ischemic, but is based on hyperemia with prolonged retardation. It is moderate but focal, so that most of the kidney is still left to carry on renal function. In malignant nephrosclerosis, the process is focal and irregular, but so severe is the vascular upset that renal function is stopped and necrotic lesions appear. So rapid is the onslaught that cases are rarely found in the transitional stages before the condition has led to death from uncomplicated uremia. Occasionally, benign nephrosclerosis may be found in which there is a single necrotic lesion or

which on the verge of an impending, malignant acceleration of the renal, vascular, prestatic process is carried off by some vascular or extra-vascular complication affecting some other vital organ

There is thus no fundamental difference between the pathogenesis of benign or malignant nephrosclerosis or even of glomerulonephritis. In all, there is hyperemia in the sense that because of peripheral vascular dilatations a greater quantity of blood is present at any one time, and ischemia in the sense that the flow of blood is markedly retarded through the involved vessels. In pathogenesis, nephritis and benign and malignant sclerosis are based only on varying degrees of speed and diffuseness of the same vascular mechanism of hyperemia with retardation.

The differences in etiology are unknown. In one of the cases reported miliary tuberculosis seems to have induced the severe prestatic changes that led to malignant sclerosis. In another case, pyelonephritis may have done the same. Volhard³³ suggested a constitutional or acquired angiospastic factor, with circulating epinephrine or peptones as its ultimate cause. Ask-Upmark's five cases of juvenile malignant nephrosclerosis indicate the existence of some inherited endogenous predisposition. Whether or not there is some toxin as the ultimate cause of the excessive stimuli which produce the malignant angiospasm and extreme vascular dissociations and what that toxin may be is not as yet determined and cannot be answered in this paper. Lead has been suggested³⁴. Plumbism accelerates vascular sclerosis, but does not lead especially to malignant sclerosis. Syphilis has long been accepted as an important factor of nephrosclerosis in general. Fahr considered it especially important in malignant nephrosclerosis. Herxheimer, Aschoff, Volhard, Keith and his associates³⁵ and Klempeier and Otani, working perhaps with different material, could not confirm this theory. The material in this paper indicates that syphilis predisposes to nephrosclerosis in general, but not to malignant nephrosclerosis in particular. Fahr considered rheumatic arthritis important. A diet high in proteins³⁶, gout, diabetes, alcohol and tobacco have all been suggested, but not proved, as factors.

33 Volhard, F. *Die doppelseitigen hematogenen Nieren-Erkrankungen*, Berlin, Julius Springer, 1918.

34 Battaglia, F. *Il rene saturnino*, Policlinico (sez. med.) **34** 153, 1927.
 Pejic, S. Nature of Primary Renal Lesion Produced by Lead, *Ann. Int. Med.* **1** 577, 1928.

35 Keith, N. M., Wagner, H. P., and Kernohan, J. W. The Syndrome of Malignant Hypertension, *Arch. Int. Med.* **41** 141 (Feb.) 1928.

36 Nuzum, F. R. Changes in Kidney in Animals with Increased Blood Pressures while on High Protein Diets, *Arch. Int. Med.* **40** 364 (Sept.) 1927.

Whatever its etiology, the pathogenesis of malignant nephrosclerosis begins with the advent of a generalized arterial hypertonicity, which brings with it hypertension. The hypertension, at first transient, later becomes more or less permanent and may continue for years without further changes in the arteries. The heart hypertrophies. Studies of the nail beds show inconstant changes in the capillaries (Kylín,³⁷ Volhard³⁸ and Klingmüller³⁹). Whether or not sclerosis develops in the arteries and which vascular bed is selected depends, not on generalized arterial hypertonus itself, but on local, peripheral, vascular dissociations.

If these dissociations affect the kidneys in particular (the kidneys are particularly susceptible because of their double capillary system and excessive functional strains) and if they affect them moderately, a benign nephrosclerosis slowly develops. With this atherosclerosis *renum lenta*, renal function is still fairly well maintained, though there may be transient periods of relative insufficiency as the process slowly and erratically progresses (Klein,⁴⁰ Major⁴¹ and Mark⁴²). In this prodromal, hypertonic stage, the patients are sturdy, plethoric and healthy, despite their permanent high blood pressure. They may continue to engage in heavy manual labor, and the only warning of the malignant character of the hypertension may be an albuminuric retinitis, which may appear even a year before the fatal issue. The robust ruddiness of these patients suggested to Volhard the clinical term of "red" hypertension. Most of these cases are terminated by cardiac failure, coronary accident, cerebral vascular accident or some vascular accident.

With this predisposing basis, after a long or short prodromal period, the remaining cases slowly or rapidly progress to malignant nephrosclerosis. The same but more violent, etiologic, toxic-irritative factor or some other etiologic factor rapidly releases an exaggeration of the same vascular dissociations with more marked retardation hyperemia. Focal, proliferative, exudative, degenerative and finally necrotic lesions result in the development of atherosclerosis *renum accelerata*. Studies of the nail beds show intermittent vascular spasms and even organic changes. This is the terminal hyperkinetic stage. The marked vascular upset

37 Kylín, E. Studien über das Verhalten des Kapillardrucks im besonderen bei arteriellen Blutdrucksteigerungen, *Zentralbl f inn med* **41** 505, 1920.

38 Volhard, F. Bemerkungen zu der vorstehenden Mitteilung von Kylín, *Zentralbl f inn Med* **41** 512, 1920.

39 Klingmüller, M., and Nevermann, H. Capillarstudien, *Ztschr f d ges exper Med* **66** 734, 1929.

40 Klein, O. Ueber die Rolle der transitorischen Niereninsuffizienz im Krankheitsbild der arteriosklerotischen Hypertonie, *Med Klin* **22** 1212, 1926.

41 Major, R. H. Kidneys in Arterial Hypertension, *Am J M Sc* **176** 637 1928.

42 Mark, A. E. Kidneys and Arterial Hypertension, *M I & Rec* **131** 206, 1930.

throws the kidneys out of function. Chemical examination of the blood discloses marked nitrogenous retention. The patients turn weak, toxic and markedly anemic. The "red" hypertension of Volhard thus changes to a "pale" hypertension, as absolute renal insufficiency closes the nephrosclerotic picture with uremia.

CONCLUSIONS

There is no fundamental difference in the pathogenesis of benign and malignant nephrosclerosis, whatever their respective etiologies may be. Both depend, however, not on glomerular ischemia or on arteriolar occlusion, but on a hyperemia associated with a retardation of flow. This conclusion was suggested by a histologic study, checked by a series of experimental injections. The retardation is based on a neurogenic dissociation in reaction between arterial constriction and peripheral dilatation. The changes that follow are analyzed on the basis of Ricker's views on renal hemodynamics. Moderate retardation leads slowly to the organic changes of benign nephrosclerosis. Severe retardation rapidly induces the pathologic changes of malignant nephrosclerosis and terminates in uremia. Malignant nephrosclerosis is therefore accepted simply as an "atherosclerosis renum accelerata gravis."

BODY TYPES IN WOMEN OF INFERTILE CONSTITUTION

THE VALUE OF SURFACE AREA PROPORTIONS AS AN ANTHROPO-
METRIC METHOD OF DIFFERENTIATION *

SAMUEL GORDON BERKOW, M D

PERTH AMBOY, N J

Reproduction, metabolism and growth are not wholly independent activities of the body. Throughout life they exert a varying influence on one another¹. The relation is not always apparent, yet conception, the supreme moment of sexual activity, is the most potent of the stimuli of growth. It initiates an orderly extension and division of the mass which are not ended even at maturity, for in the phenomenon of repair they continue, with diminishing force,² throughout life.

The relation between the generative and vegetative functions is not direct. On the strongest evidence, the mediacy of endocrine glands is assumed. At puberty, entrance of a sex hormone secretion into the body economy is accompanied by rapid growth, both general and sex specific, and by changes in the configuration of the body³. However, according to Nicola Pende,⁴ pure, dominant, constitutional insufficiency of the sex glands is seldom found. More frequently encountered are "constitutional anomalies of other endocrine glands which have a very great influence on sexual development, such as the hypophysis, thyroid, thymus, the adrenals or the pineal body". In Ruffini's apt phrase, form is the plastic image of function, for these glands influence the sex glands or the sex organs on the one hand, and growth and configuration of the body on the other.

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* From the Gynecological Service, Mount Sinai Hospital, New York, Endocrine and Sterility Clinics

1 Frank, R. T. The Female Sex Hormone, Springfield, Ill., Charles C. Thomas, 1929, p. 7. Schroeder, R. Deutsche med. Wchnschr. **55** (Jan 4) 1929, abstr., Surg. Gynec. Obst. **50** 26 (Jan) 1930.

2 Demonstrated mathematically by Carrel, Du Nouy and Hartman. Cicatrization of Wounds, J. Exper. Med. **24** 429 and 451 (Nov) 1916.

3 The surface area proportions at puberty have been investigated by me in the public schools of Perth Amboy, N. J., the Kiddie Keep Well Camp of Middlesex County (N. J.), and at private camps, with the cooperation of J. Peretzman, M. D., Fanny Sender, M. D., Murray Jacobson, B. A., and Edward Margaretten, B. Sc.

4 Pende, Nicola. Constitutional Inadequacies (translated by S. Naccarati), Philadelphia, Lea & Febiger, 1928, p. 200.

The first influence is internal and is expressed in altered functions, in the instance under consideration, infertility. The second influence is external and visible. Moreover, the various glands that are known to influence the body type do so in a definite and characteristic manner.

The association of infertility with certain body types was noted by Hippocrates.⁵

Women may be judged of whether they are in a fit state for conception or not by attending the following circumstances: in the first place to their shapes. Women of smaller stature more readily conceive than taller persons; the thin than the fat.

Karl Pearson,⁶ brilliant co-founder with Frances Galton of the science of biometrics, concluded from statistical studies that tall women procreate faster than small women. This contradiction is more apparent than real, for recently Frank⁷ distinguished four types among infertile women, to which the vast majority conform: (1) the typical, normal feminine, (2) the infantile, (3) the neuter and (4) the pseudomascu-line. Dr Frank's observations concur with modern conception of the influence of the endocrine glands.

In the present investigation I sought to apply a clinically available anthropometric method to Dr Frank's material. For reasons to be stated presently, the requirements seemed to be met by Du Bois's⁸ linear formula for the determination of the surface area, and especially by the proportions derived therefrom.

The advantages of mathematical expression are too obvious for discussion. It must be noted, however, that the method pursued is not exhaustive. Not all of Dr Frank's observations are thus quantitatively expressed. Histories, height and thickness of the symphysis pubis and the height of the palate arch, for instance, are not measured. Less tangible similarities and differences, often difficult even to state clearly, must always remain to the perception and astuteness of the diagnostician, yet the method has the advantage of its limitations, for more complicated mathematical data would be a distinct disadvantage.

The surface area proportion method provides a fairly simple clinical means of expressing exactly and adequately certain fundamentals of bodily build and symmetry.

5 Adams, F. The Genuine Works of Hippocrates, New York, William Wood & Company, 1921, vol. 1, p. 220.

6 Pearson, quoted by Garrison, F. H. History of Medicine, ed. 2, revised, Philadelphia, W. B. Saunders Company, 1917, p. 708.

7 Frank, R. T. Endocrine Causes of Sterility in Women, Surg. Gynec. Obst. **45** 189 (Aug.) 1927.

8 Du Bois, Delafield, and Du Bois, E. F. Clinical Calorimetry. The Measurements of the Surface Area of a Man, Arch. Int. Med. **15** 868 (May) 1915.

The purpose of this investigation was therefore twofold (1) to test the method under clinical conditions and, at the same time, (2) to differentiate and group by this means the body types of women of infertile constitution

Fifty cases of primary sterility were available for this study. Each case had been thoroughly worked up by the staff of the sterility clinic. The male partner had been exonerated by the Huhner test, many actively motile spermatozoa being recovered from both the vagina and the cervix. Pelvic examination gave negative results except for hypoplasia in 28 per cent of the cases. One or more Rubin tests demonstrated the patency of the tubes, tubal peristalsis, recorded by the kymograph, was not equally active in all cases. Special investigations, for the most part ordered by the staff of the endocrine clinic, included blood counts, basal metabolism, roentgenograms of the sella turcica, visual fields and examinations of the color vision, the Janney test for carbohydrate metabolism and determination of the female sex hormone. Investigations were possible in a large proportion of the cases.

To the group complaining of sterility I have added nineteen single women referred to the endocrine clinic for severe grades of amenorrhea. Rubin⁹ recently discussed the association of long delayed and scanty menses with sterility. In a large series, he found that

Menses are habitually delayed or scanty in 35 to 8 per cent of gynecologic patients and in about 10 per cent of patients whose marriage is sterile. These patients are more apt to be sterile than normally menstruating women, the primary sterility varying between 30 and 70 per cent, and the total sterility, including secondary sterility, amounting in some groups to as high as 93 per cent.

In the present series of fifty selected cases of nonmechanical primary sterility, eighteen presented serious menstrual deficiency (36 per cent). Amenorrhea, oligomenorrhea and hypomenorrhea, of the serious grades, are often associated with lowered fertility.

Of the nineteen single women in this series, two had primary amenorrhea, one had had amenorrhea for fifteen years, three had had amenorrhea for one year or more (of these, one girl, 19 years old, had menstruated twice), three had had amenorrhea for from six months to one year and the remainder complained of oligomenorrhea and habitual amenorrhea of from six weeks to six months' duration. In this group there were several well marked types, which was an additional reason for its inclusion.

⁹ Rubin, I. C. Ovarian Hypofunction, Habitually Delayed and Scanty Menstruation, in Relation to Sterility and Lowered Fertility, *Am J Obst & Gynec.* 18: 603 (Nov) 1929.

METHOD

The surface areas of the seven chief natural divisions of the body are determined by the linear formula of Du Bois⁸ These divisions are the head (including the neck), the trunk, the arms, the hands, the thighs (including the buttocks), the legs and the feet From two to four measurements, lengths and circumferences, mostly from bony points, are made on each part, there being nineteen measurements in all From these, the surface areas are computed, a constant being used for each part, which has been determined by experiment From the actual surface areas and the total surface of the body (the sum of the seven

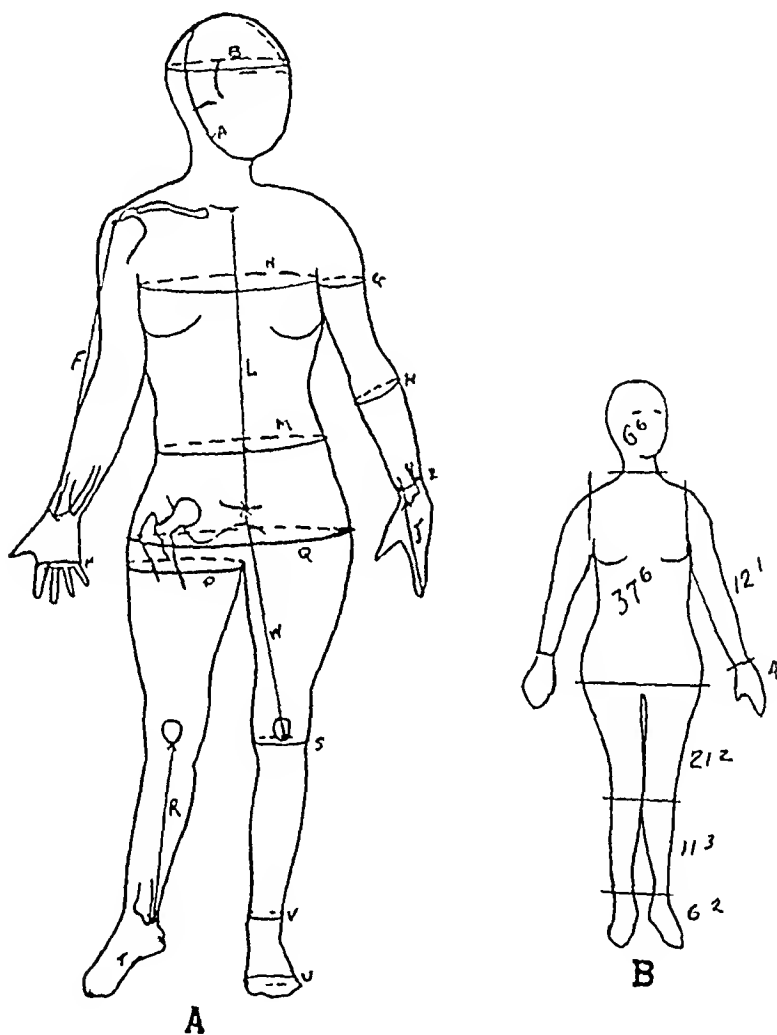


Fig 1—Method of obtaining measurements of surface area (after Eugene F Du Bois and Delafield DuBois) *A* shows the method of obtaining measurements, *B*, the surface area proportions in normal persons (not the "normals" of the present series) (From the author's illustration in Frank, R T *The Female Sex Hormone*, Springfield, Ill, Charles C Thomas, 1929)

parts), ratios of the parts, or the surface area proportions, are easily calculated (fig 1)

The direct measurements of the length and circumference of each part, from which the actual surface is computed, express a relation within the parts The actual surface areas of the parts from which the proportions are determined furnish information on each part considered by itself Finally, the surface area

proportions show the relation between the parts. Thus, in arriving at the surface area proportions one obtains three series of figures, each of which has been applied to the grouping of the cases.

Before stating the observations in the present series, it may be well to review briefly the information at hand before this study began.

In the first place, references to the proportions alone were found. I do not know of any previous study in which relative and actual areas and direct measurements were used.

The proportions were known to be sufficiently constant in healthy persons to permit the establishment of normal average proportions.¹⁰

It was known that age primarily and then nutrition and sex influence the surface area proportions.

1. From birth¹¹ to about 18 years, the proportion of the head varies inversely to the age (from 18 to 6.5 per cent), and that of the lower extremities, progressively with the age, whereas the proportion of the trunk shows a slight gradual decline (from 38 to 36 per cent), and that of the upper extremities, a slight increase.

2. The proportion of the head, relative to the total surface of the body, varies inversely as the state of nutrition: the stouter the person, the smaller is the proportion of the head. This seems to be true also of the proportion of the lower extremities. As is to be expected, the proportion of the trunk varies directly as the state of nutrition. There is no evidence of a noteworthy influence of nutrition on the ratio between the surface area of the upper extremities and of the whole body. The surface area proportion of the hands relative to the total for the upper extremities varies inversely as the state of nutrition.

10. C. R. Bardeen (The Height-Weight Index of Build in Relation to Linear and Volumetric Proportions and Surface Area of the Body During Post-Natal Development (Contributions to Embryology, no. 46), Bull. Carnegie Institute 9: 501, 1920) quoted the great Belgian anthropologist, Quetelet, who obtained, from actual measurements of the entire surface, the surface area proportions in a considerable group of people: "At a given stature and a given stage of physiological development the mean proportions of the human body are strikingly similar in diverse races. The similarities are so great that extensive careful statistical studies are necessary to prove conclusively that certain bodily proportions are characteristic of one race as opposed to another race. There is far more variation in rapidity of growth and in mean average adult stature in various races and social groups than there is in proportions of the body relative to stature at a given stage of physiological development." That these observations did not stimulate further investigations of the surface area proportions must be attributed to the extreme difficulty of obtaining surface area directly from actual measurements, by triangulation or from molds.

11. Berkow, S. G. A Method of Estimating the Extensiveness of Lesions (Burns and Scalds) Based on Surface Area Proportions, Arch. Surg. 8: 138 (Jan.) 1924.

3 The head has a larger surface area proportion in females than in males. The hands constitute a larger part of the total body surface in males (51 per cent) than in females (44 per cent), but they constitute a smaller part of the upper extremities than do the hands of the females. The thighs constitute a larger percentage of the lower extremities and of the total surface in the female than in the male. However, the legs and feet of females are smaller than those of males, both actually and in relation to the total surface. The arms of males are larger than those of females, actually and relatively.

It was suspected¹² that deviations from the normal proportions (age, nutrition and sex being considered) are caused by disturbances of the endocrine glands or by disease of the neurotrophic or osteogenic system.¹³

I arrived at these conclusions independently. I have since found that they are in entire agreement with the earlier work of Funke,¹⁴ Carl Meeh,¹⁵ Quetelet¹⁶ and all other investigators in this field. They worked

Four Groups Into Which Surface Area Proportions Fall

Group	Surface Area Proportions	Actual Surface Areas	Measurements	
			Lengths	Circumferences
1	Normal	Normal Small Normal (Male hirsuties, facial, extremities and eusecheon)	Normal Small Normal	Normal Small Normal
2	Trunk small (34%), increasing distal to trunk	Trunk small, hands and feet large	Increased	Decreased
3	Trunk large (to 48%), head small, hands and feet small	Trunk large (upper, shoulder girdle obesity)	Decreased	Increased
4	Thighs large	Thighs large (lower, pelvic girdle obesity)	Decreased	Increased

with fewer cases, but far more laboriously, as they did not have the benefit of the Du Bois linear method.

NEW DATA ON FEMALE CONSTITUTIONAL INFERTILITY AND SEVERE AMENORRHEA GROUPED ON THE BASIS OF SURFACE AREA PROPORTIONS AND ASSOCIATED DATA

On the basis of surface area proportions, the cases studied fall into four groups. A subgroup is distinguished by means of the associated data, i. e., actual surface areas and direct measurements (accompanying table).

¹² Berkow, S. G. Disturbed Surface Area Proportions in a Case of Suspected Ovarian Hyperfunction, *J. A. M. A.* **88** 1953 (June 18) 1927.

¹³ Unpublished investigations by me at Montefiore Hospital, New York.

¹⁴ Funke. Moleschotts Untersuchung, *Naturlehre* **4** 36, 1858.

¹⁵ Meeh, Carl. Oberflachenmessungen des menschlichen Korpers, *Ztschr. f. Biol.* **15** 425, 1879.

¹⁶ Quetelet. Des proportions du corps humain, *Bull. Acad. roy. d. sc.* **15** 580, 1870.

Group 1 (Eumorphic—Fifty-four Cases)—The proportions are within the range encountered in normal adult females and also conform to the proportions of a small control group (ten) measured in the contraceptive clinic at Mount Sinai Hospital. For these reasons and because the configuration that yielded these proportions seemed “right” to the unaided view, group 1 is considered eumorphic and its proportions “normal.”

However, this group is not uniform as to associated physical data or as to associated symptoms. One subgroup is distinguished (three cases) in which the total surface of the body is remarkably small. The actual areas of the parts and the lengths and circumference by actual measurement are small, but normal ratios are preserved. These women were, of course, short (from 4 feet, 10¼ inches to 4 feet, 11 inches), their weight varied from 112 to 124 pounds (50.8 to 56.2 Kg). Two of

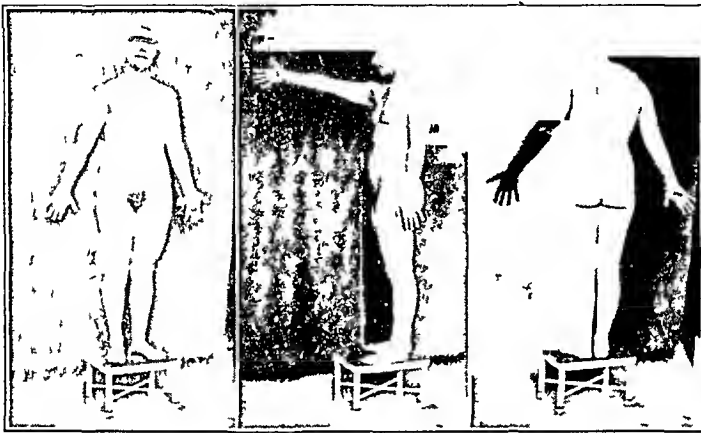


Fig 2—E A, group 1, subgroup 1. The proportions are normal, the actual surfaces are small, and the measurements are small.

the women (aged 26 and 27) had never menstruated, and the third had menstruated four times in the past five years. Secondary sex characteristics were present. The genital organs, particularly the cervix and the body of the uterus, were extremely hypoplastic. In two the sella turcica appeared smaller than normal, and in one there was marked bridging between the anterior and the posterior clinoid process. In all three cases, the female sex hormone was absent from the blood, and in only one was it found in the urine.

A second subgroup (six cases) is distinguished by the masculine character and distribution of hirsuties. This subgroup is included for purposes of classification, although it is not distinguished by the surface area proportions or the associated data of that method. These women were a little taller than those of the first subgroup (from 5 feet, ¾ inch to 5 feet, 2 inches), and their weight was correspondingly greater. The total surface of the body averaged about 1,000 sq cm more than

that in the first subgroup Menstruation was regular in one case, habitually delayed in three cases, and in two cases the patients had been amenorrheic as long as one year. The breasts were large and flabby or had flat nipples. The symphysis pubis was high and thick. The distinguishing characteristic was the male escutcheon and the presence of coarse hairs on the face and extremities, especially the lower extremities. The uterus was small, retroverted or retroflexed, and one of the women had a uterus didelphys and a double vagina. Roentgenograms of the sella turcica were negative. The basal metabolism was minus 12 per



Fig 3—M R, group 2

cent in one case, and minus 27 and minus 40 per cent in one other case, it was normal in the other cases.

Group 2—(Two Cases)—In these two cases the proportions of the trunk were very small (34 per cent and 34.3 per cent), whereas those of the head and the extremities were relatively large. Bichat called this type the hypovegetative or animal type ("the morphological differentiation and the animal system preponderate over the total mass and the vegetative system"—Pende), and Viola termed it the microsplanchic type. This type of configuration is also called the longitypical, dolichomorphic, hyperevolute and, I believe, eunuchoid. The parts farthest from the trunk have the greatest increase in their proportions. Thus, the hands are large for the arms, the feet are large for the legs, and the legs are large for the thighs. The actual surface of the head and

extremities is not large. The actual measurements show an increase in the lengths and a decrease in the circumferences as compared to all groups. They show that the disproportions are due to increases in length.

Both of these women had primary amenorrhea (aged 26 and 18). They were 5 feet, 5½ inches and 5 feet, 3½ inches, respectively, in height, and weighed 113 and 117 pounds (51.3 and 53.1 Kg). One had male breasts, the other had small breasts with supererogatory nipples. The latter patient had a total absence of pubic hair and no hair in the axillae, but the hair covering her scalp was fine, long and abundant.



Fig 4—J C, group 2

The genitals were infantile. The female sex hormone showed a monthly cycle in one case, its presence had not been reported in the other case. Roentgenograms of the sellae turcicae showed them to be normal in size and contour. The basal metabolisms were normal.

Group 3—(Seven Cases)—In this group the proportions of the trunk are the greatest. All of the other proportions are small, becoming smaller in the parts distal to the trunk. The average proportions are head, 5.5 per cent, trunk 45.5 per cent (limits, 43.7 and 48.4 per cent), arms, 12.2 per cent, hands, 3.7 per cent, thighs, 17.7 per cent, legs, 9.9 per cent, feet, 5.1 per cent. The women in this group would be described as brachymorphic, hypervegetative (from the fact that the

trunk contains the organs of vegetation), hypo-evolute (not so from the surface area proportions) and of the Frohlich type

Of the actual surfaces, that of the trunk is outstandingly great (average, 9,113 sq cm), compared to other groups. The other surfaces correspond to those of other groups. They are small only when compared to the total surface of the body, the enormous surface of the trunk or the body weight.

Of the actual measurements, M , N and Q (fig 1) are large, particularly M and N . The circumferences of the extremities are large near the trunk, particularly when compared to the length.

In this group the women were short (average, 4 feet, 10 inches), and stout (average weight, 184 pounds [83.5 Kg]). On inspection, the

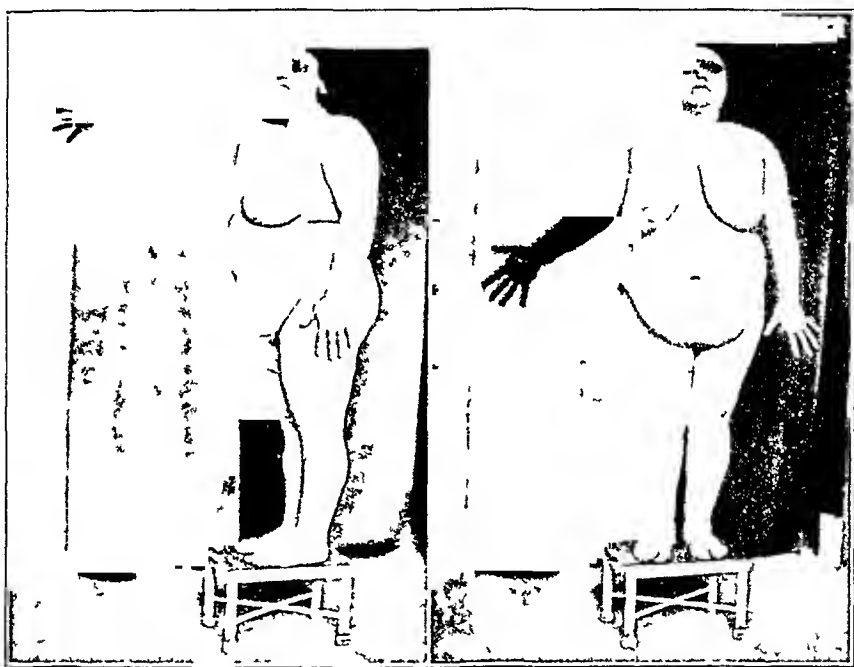


Fig 5—R M, group 3

obesity was chiefly of the trunk and upper (shoulder) girdle variety. This was best seen from the posterior aspect. Secondary sex characteristics were present. The breasts were large and flabby. The growth of hair was normal, or with the male type of escutcheon.

The menses were irregular and habitually delayed in three cases, in one patient menstruation occurred about once a year, two patients had been amenorrheic for one and a half years, and one had not menstruated in fifteen years.

Pelvic examination gave negative results or showed moderate genital hypoplasia.

In one of the women (J J, fig 6) there was positive evidence of a pituitary tumor, for which the patient was treated by operation and deep roentgen therapy at the Mount Sinai Hospital. At the time of

writing this article, roentgen examination showed the operative defect in the floor of the sella turcica. In all other cases, roentgen examination did not demonstrate any definite abnormality of the sella turcica, as to size and contour. Examination of the eyes, the fundi, the visual fields and color vision gave negative results. The carbohydrate metabolism was high in only one case (J J). The basal metabolism varied between -12 and $+9$ per cent.

Group 4—(Sia Cases)—In this group the women are also short and stout. Like the women in the preceding group, they would be described as brachymorphic, hypervegetative and hypo-evolute. In addi-

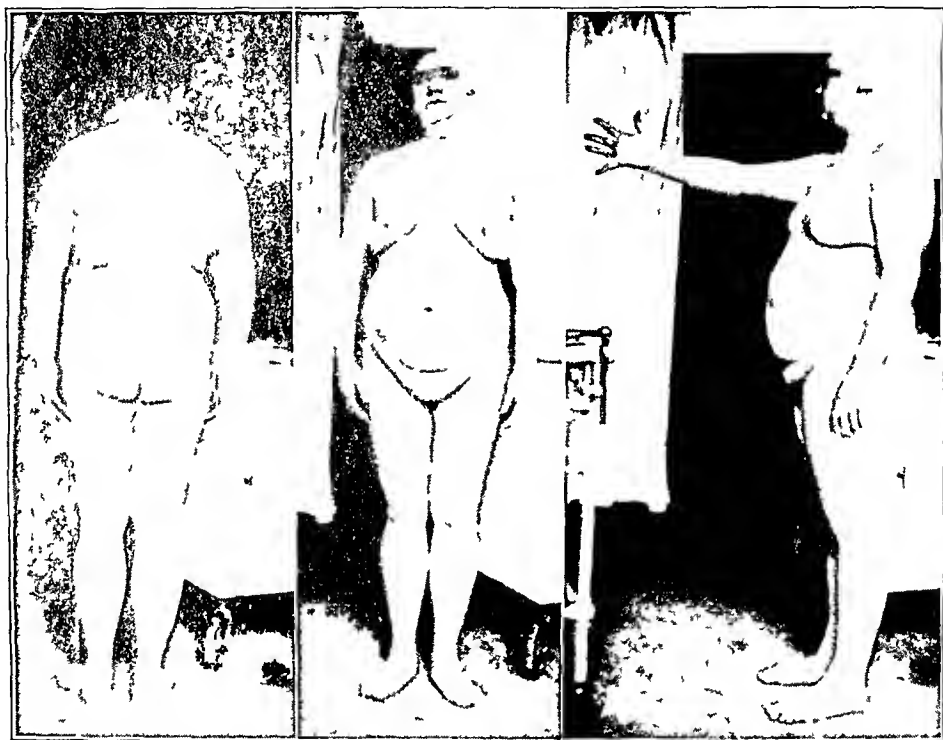


Fig 6—J J, group 3. There was a pituitary tumor.

tion to a large trunk, the women in this group possess heavy lower extremities and the obesity is chiefly of the lower (pelvic) girdle type.

The surface area proportion of the trunk is large, but is less than that in group 3. The proportions of the thighs, legs and feet are larger than in the preceding group and are within the range of my norm. The surface area proportions of the head, arms and hands are as in group 3.

On comparison of the actual surfaces with those in group 3, that of the trunk is considerably less in this group (average, 7,625 sq cm), the surfaces of the thigh and the legs are similar to those of the preceding group, the surfaces of the feet are larger than in group 3.

Of the three circumference measurements *M*, *N* and *Q* (fig 1), the last is greatest in every instance in this group, whereas in group 3, *N*

is the greatest measurement. Only Q is as great in this group as in group 3, M and N are less.

The average height of the women in this group was 5 feet, 2 $\frac{7}{8}$ inches, the average weight, 174 pounds (78.9 Kg). In four of the six women the gain in weight had taken place soon after marriage. Three women gained from 40 to 50 pounds (18.1 to 22.7 Kg) each within two years after marriage.

These women showed a tendency toward hirsuties. The pubic hair was more male than female in distribution. The breasts were well developed, in one instance, there was marked asymmetry, the left breast being infantile, the right normal. The pubic arch was high and heavy.

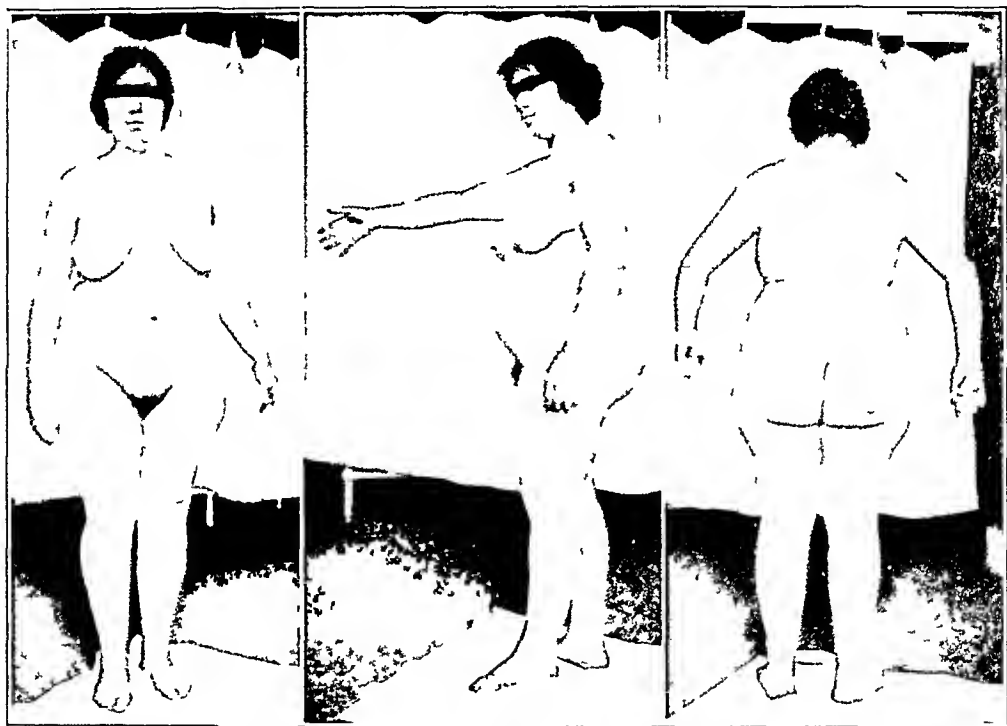


Fig 7—M C, group 4

Four women were described as masculine in appearance, two as feminine. The "masculine type" of women had heavy superciliary ridges, rather coarse features and darker coloring of the skin.

Severe grades of amenorrhea are met in this group, from irregular menses about every five or six weeks to amenorrhea of three and one-half years' duration.

Pelvic examination revealed moderate to marked hypoplasia.

Studies of the female sex hormone were conducted in three cases. One patient had a subthreshold cycle, and in a second the female sex hormone was absent (R. L., aged 25, had been amenorrheic for three and one-half years). In another case the Rubin test demonstrated patency of the fallopian tubes, but without tubal contractions. At 10 pounds

of pressure, the column of mercury rose to 108 and gradually dropped to 80, fluoroscopy showed a subphrenic pneumoperitoneum (Dr Mintz). The basal metabolism was within normal limits. The sugar tolerance was normal. No enlargement of the pituitary gland was shown by the x-rays, and the fundi, visual fields and color vision were normal in every case.

COMMENT AND SUMMARY

An anthropometric and clinical study of sixty-nine "constitutionally sterile" women has been presented. It is noteworthy that male responsibility was eliminated solely on the number, motility and shape of sper-

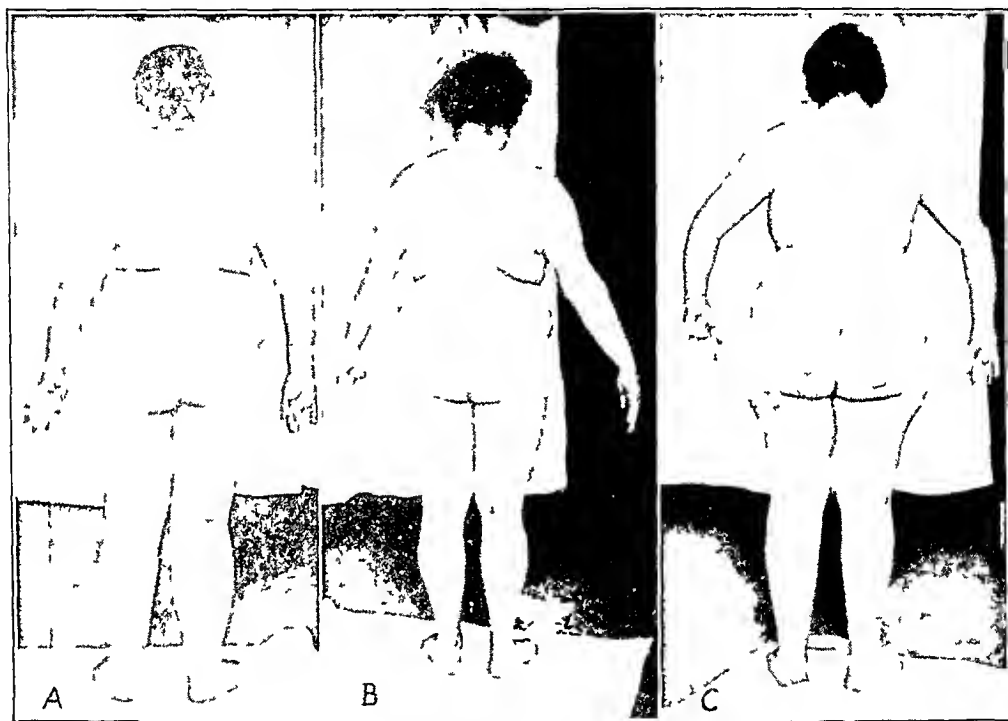


Fig 8—*A* shows generalized obesity in an acromegalic woman, *B*, upper (shoulder) girdle obesity (group 3), *C*, lower (pelvic) girdle obesity (group 4)

matozoa in postcoital specimens. Constitutional factors in the males, which may, conceivably, affect the quality or potency of the spermatozoa, were not included in this investigation. The objection may therefore be raised that having failed to establish a mechanical cause in either the female or in the spermatozoa, the blame has been placed arbitrarily on the woman's constitution. This criticism has some merit. A constitutional study of the male partners is greatly to be desired. On the other hand, when abnormal configuration of the body and other endocrine stigmas are demonstrated in the female, it is fair to assume that the responsibility does rest largely with her.

On the basis of the surface area proportions, four groups were differentiated, of which three are considered abnormal. In the normally proportioned group, one subgroup was distinguished by its small actual surfaces and small measurements. Menstruation, secondary sex characteristics, pelvic examination and laboratory observations were found

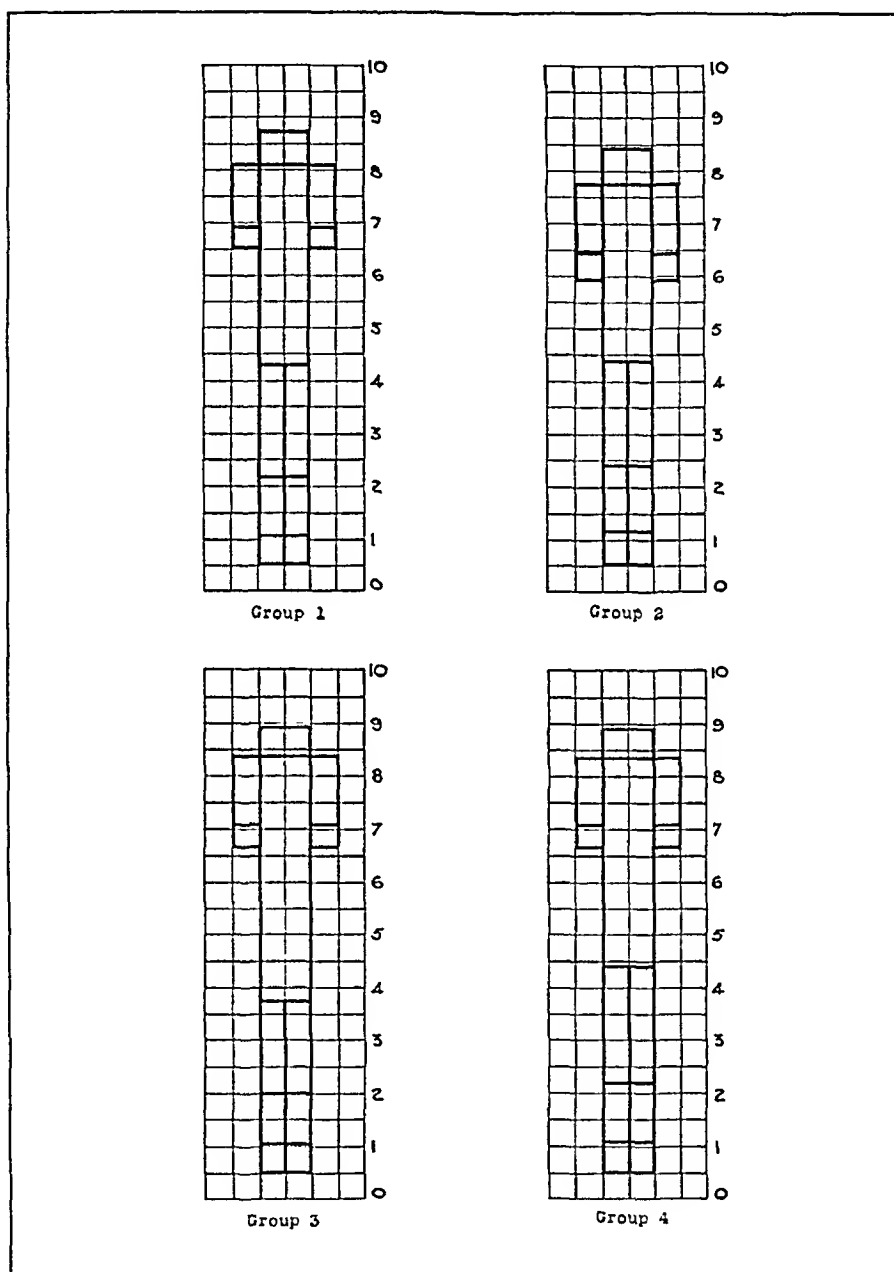


Fig 9—A graphic presentation of the surface area proportions in the four groups. The figures are drawn to scale.

to vary less within the groups than between the groups, however, the influence of various glands, to different degrees, was seen in each group. It has not been possible to introduce all evidence against the derangement of the dominant gland in each group. To uncover a little more the culpability of the dominant gland, it would be necessary to intro-

duce further nonsterile cases for comparison. A number of such cases of patients with menorrhagia, acromegalia, hyperthyroidism and hypothyroidism, are available. For the sake of lucidity, they are kept for a later presentation.

With very few cases in each group and each group complicated, to some extent, by a different gland and by a different degree of glandular influence, the wisdom of being categorical may be questioned. It must be remembered that the field of human constitution is a terrain of "many signs and few guide-posts." Any direction, however vague, may prove helpful. Furthermore, this classification is considered, to change the metaphor somewhat, not as a permanent framework, but as a preliminary sketch.

The cases have the further advantage of a thorough work-up. For this credit belongs to the staffs of the endocrine and sterility clinics and to the laboratory and the x-ray and eye services.

The more general object of the study, to determine the clinical availability of the surface area proportions as a means of anthropometric differentiation, seems to have been fully attained. The study has been carried on in active clinics within a narrow allotment of time. The usual routine was not interfered with. Without special instruments and by means of simple arithmetic, a mathematical formula has been reached which is complete in itself and is expressive of certain fundamentals concerning the configuration of the body. The value of this expression can be ascertained only through further study. The greatest need at present is to establish normal standards of height-weight, sex and the stage of physiologic development considered.

INFLAMMATION

A PROTECTIVE MECHANISM *

VALY MENKIN, M D

BOSTON

Although most pathologists are agreed as to the general character of inflammation, various definitions of this fundamental pathologic process have been offered. Some define inflammation merely as the reaction of tissues to injury. Others, following the lead of Cohnheim, define it as the reaction affecting specifically the wall of blood vessels after injury, i e, the increased permeability that allows the escape of plasma and blood corpuscles into the surrounding tissue. By some, notably Cohnheim¹ and Adam,² inflammation is viewed as a process adapted to reduce the harmful consequences of an injury, Metchnikoff, Maichand and Councilman regarded it solely as a reaction excited by the presence of something injurious to the tissue. Opie³ defined it as a process by means of which cells and serum accumulate about an injurious substance and tend to remove or destroy it. In the course of this presentation, an attempt will be made to give evidence showing that before and during its removal or destruction, the injurious substance is circumscribed and fixed in situ by the inflammatory reaction.

The process of inflammation, from this point of view, does not include the repair or regenerative changes of healing that follow the inflammatory reaction.

The cardinal symptoms of inflammation (heat, pain, redness and swelling) are perhaps best illustrated by the ordinary boil or by the lesion of erysipelas. The etymology of the word indicates that earlier writers attached primary significance to the increased heat of the inflamed part. In an inflamed area, the normal functional equilibrium between cells, intercellular fluids and blood is doubtless profoundly modified. Local physiologic changes are involved affecting the permeability of

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* From the Henry Phipps Institute of the University of Pennsylvania and the Department of Pathology of the Harvard Medical School

1 Cohnheim, J. Virchows Arch f path Anat **40** 1, 1867

2 Adam, G. J. Inflammation, London, Macmillan and Company, 1909

3 Opie, E. L. Inflammation, Arch Int Med **5** 541 (June) 1910, J Immunol **17** 329, 1929

capillaries, the rate of blood flow and the balance of body fluids. Increase of capillary permeability is shown by local edema. The proteins of the plasma to a varying extent pass out into the tissue spaces, disturbing, doubtless, the osmotic relationship between tissue fluids and blood plasma. About thirty years ago, Adler and Meltzer⁴ concluded that the passage of fluids from tissue spaces into lymphatics probably depends on osmosis, perhaps assisted to some extent by filtration. Starling⁵ pointed out that capillary filtration is the resultant of two forces: capillary pressure on the one hand and the osmotic pressure exerted by the plasma colloids on the other. Recently this conception has been confirmed experimentally by the work of Landis⁶ who showed by measuring directly intracapillary pressure that the rate of filtration depends on the difference between capillary pressure and the osmotic pressure of plasma colloids. By this direct method he proved that whereas filtration occurs at the arterial end of capillaries, absorption from tissue spaces takes place at the venous end. The normal filtration equilibrium of the capillary wall is modified in inflammation by the passage of plasma proteins into the tissue spaces. If the passage of lymph from tissue spaces into afferent lymphatic vessels depends largely on an osmotic equilibrium, it is probable that the accumulation of plasma proteins in the tissue spaces will modify and retard the flow of lymph into the afferent lymphatic vessels. Schade and Menschel⁷ found that in inflamed areas, especially those with suppuration the accumulation of products of disintegration of the tissues may become so great that the osmotic pressure is raised as high as eleven atmospheres. An inflamed area can be considered as shunted off from the rest of the organism. It has its own metabolism, its own hydrogen ion concentration and as was just pointed out, its own modified circulation.

FIXATION OF FOREIGN SUBSTANCES AT THE SITE OF INFLAMMATION

Throughout the remainder of this discussion, one phase of the reaction will be emphasized, i.e., the fixation of foreign substances by the inflammatory process. This is a function that is evidently of great importance as a mechanism of protection to the organism as a whole.

The dissemination of foreign substances from the site of injection into the lymphatics and the blood stream has been studied by various investigators. Muscatello⁸ showed that carmine and various other

4 Adler, I., and Meltzer, S. G. *J. Exper. Med.* **1** 482, 1896.

5 Starling, E. H. *J. Physiol.* **19** 312, 1895-1896.

6 Landis, E. M. *Am. J. Physiol.* **81** 124, 1927.

7 Schade, H., and Menschel, H. *Ztschr. f. klin. Med.* **96** 279, 1923.

8 Muscatello, G. *Virchow's Arch. f. path. Anat.* **142** 327, 1895.

inert particles when injected into the peritoneal cavity reach the anterior mediastinal lymph nodes rapidly Buxton⁹ found that when typhoid bacilli were injected into the peritoneal cavity they appeared in the blood stream in great numbers within a few minutes Wells and Johnstone¹⁰ demonstrated that the absorption from the peritoneal cavity takes place through lymphatic vessels

Within recent years, evidence has accumulated indicating that an inflammatory reaction at the site of injection might be a factor in delaying the passage of foreign substances into the circulating blood Noetzel¹¹ demonstrated that the injection of bacteria (*B. pyocyaneus*) into the knee joint of rabbits was followed by a rapid dissemination of the micro-organisms which could be recovered five or ten minutes later from the inguinal, crural and lumbar lymph glands Pawlowsky¹² repeated Noetzel's experiment and also injected staphylococci into a knee joint that had been previously inflamed by a sterile irritant such as turpentine or alcohol The dissemination of the bacteria was either inhibited or wholly prevented by the acute inflammatory reaction These observations have been confirmed Opie¹³ showed that a foreign protein injected into the skin of an immunized animal is fixed at the site of injection where the contact of antigen and antibody causes an acute inflammatory reaction (phenomenon of Arthus) In normal animals, on the contrary, foreign proteins when injected into the skin produced little if any inflammatory reaction and readily penetrated into the blood stream Recently the same investigator demonstrated that acute inflammation of the peritoneal cavity caused by a sterile irritant, aleuronat, retards the rush of injected hemolytic streptococci from the peritoneal cavity into the circulating blood stream After the inflammation has lasted twenty-four hours, the passage of bacteria from the peritoneal cavity is completely prevented

Gay¹⁴ and his collaborators studied the changes in resistance to intrapleural inoculation of streptococci after a sterile inflammation had been previously caused by various irritants They contended that the increased resistance to the pathogenic micro-organism results from the accumulation of plasmatocytes This interpretation was recently questioned by Opie,¹⁵ who maintained that there are as yet no data that will

9 Buxton, B. H. J. M. Research **16** 17, 1907

10 Wells, H. G., and Johnstone, O. P. J. Infect. Dis. **4** 582, 1907

11 Noetzel, W. Beitr. z. klin. Chir. **51** 740, 1906

12 Pawlowsky, A. D. Ztschr. f. Hyg. u. Infektionskr. **62** 433, 1909

13 Opie, E. L. J. Immunol. **9** 259, 1924 J. Exper. Med. **39** 659, 1924

14 Gay, F. P., and Morrison, L. F. J. Infect. Dis. **33** 338, 1923

15 Opie (footnote 3, second reference)

determine the rôle of polymorphonuclear leukocytes, mononuclear cells, serum or, indeed, increased permeability of blood vessels in overcoming the injurious effects of sterile irritants or of bacteria

During the past two years I have been studying the behavior of foreign substances injected into an inflamed area, by direct observations of the tributary lymphatic nodes and vessels draining that area. After some preliminary experimentation with nucleated corpuscles in fowls, a vital dye, trypan blue, was tried and found to be satisfactory.¹⁶ If trypan blue is injected into the normal subcutaneous tissue of the fore leg of a rabbit, within from twenty to thirty minutes the dye stains the tributary afferent lymphatic vessels, the lymph node and the efferent lymphatic. If, on the other hand, the dye is injected into a similar area in which an inflammatory reaction has been produced some time before by a sterile irritant, the dye does not appear in the tributary lymphatics, the afferent lymphatics, the lymph node and the efferent lymphatic vessel remain colorless. The dye is evidently retained in the inflamed area. The fixation of the dye takes place very soon after the injection of the irritant, this reaction was observed in some instances when the dye had been injected thirty minutes after injection of the irritant.

Since trypan blue tends to remain in situ when injected directly into the inflamed area, an attempt was made, at the suggestion of Dr. Opie, to determine whether the dye injected into the blood stream would accumulate at the site of inflammation. MacCurdy and Evans¹⁷ pointed out in 1912 that the normal brain and cord always remain free from dye injected intravenously, but that areas of damage, such as softening or inflammation, become deeply stained.

Other investigators have confirmed the early observations of MacCurdy and Evans. It was found that trypan blue introduced into the circulating blood rapidly entered the site of inflammation, staining the tissue deeply, and that it did not readily drain away through the tributary lymphatic vessels. It was further observed that the longer the interval of time between the injection of the irritant and that of the dye, the more complete was its retention, less of the dye diffusing to the regional lymph node. Thus there is not only a rapid accumulation but also a fixation of dye from the blood stream in the inflamed area.

It is well known that the retrosternal lymph nodes of the anterior mediastinum drain the peritoneal cavity. If trypan blue is injected into a normal peritoneal cavity, the retrosternal lymph nodes are within a short time deeply stained with the dye, but if the dye is injected into a peritoneal cavity in which an inflammatory reaction has been set

16 Menkin, V. J. *Exper. Med.* **50** 171, 1929.

17 MacCurdy, I. T., and Evans, H. M. *Berl. klin. Wchnschr.* **49** 1695, 1912.

up by a sterile irritant such as aleurionat, the dye is wholly or partly prevented from reaching the retrosternal lymphatic nodes. Consequently, from these studies the following principle has been established. A vital dye, trypan blue, injected into the circulating blood stream rapidly accumulates in an inflamed area and is fixed there, so that it fails to appear in the tributary lymphatics draining the area.

The accumulation in inflamed tissue of the dye when introduced into the blood stream is doubtless influenced by increased capillary permeability, which is part of the inflammatory reaction¹⁸. We have been able to secure quantitative data by studying directly the change in the concentration of the dye in the blood stream both in the inflamed and in the normal mesentery of the frog.

After intraventricular injection of the dye the change in concentration of trypan blue within the capillaries may be estimated by a colorimetric method. When the logarithms of the concentrations of dye within the capillary are plotted against time, a straight line is obtained denoting an exponential type of relationship. The equations obtained by the method of least squares for both the normal and the inflamed areas were of the following type

$$y = bc - ax$$

The actual equations found were

$$(1) \text{ In the normal peritoneal cavity } y = 7.63c - 0.24x$$

$$(2) \text{ In the inflamed peritoneal cavity } y = 6.9c - 0.42x$$

y represents the concentration of dye in the capillaries as estimated by comparison with the nearest standard on the colorimetric scale and x stands for the time in minutes after the intraventricular injection of the dye, a represents the slope of the curve. In the equation for the control experiments, a was found to equal 0.24 while in the equation for the concentration of dye in the capillaries of the inflamed peritoneal cavity, a equaled 0.42. Since a is an index of the slope and consequently of the rate of change of concentration of the dye, it is clear that the rate of fall of concentration of trypan blue in the capillaries of an inflamed area is almost twice as rapid as in the capillaries of the normal mesentery. The dye obviously diffused outward into the extracapillary spaces, as can be seen by direct observation and, of course, by the fact that the dye stains the cells of the extracapillary spaces. This does not necessarily mean that the fall of concentration in dye within the capillaries is an exact measure of the amount of dye that passes through their walls, for it is conceivable that there may be other factors involved. However, in view of our previous studies, showing that trypan blue injected intravenously rapidly passes into an inflamed area, it is believed that the increased rate of fall of concentration is a measure of increased passage of dye through the capillary wall.

Landis showed that capillaries injured by alcohol and mercuric chloride are permeable to the plasma colloids and approximately seven times more permeable to fluids than the normal capillary wall. It seems probable that similarly the inflammatory irritant may have a direct toxic effect on the capillary walls and, by increasing their permeability, may cause a fall in the osmotic pressure of the plasma colloids. Such

¹⁸ Menkin, V., and Menkin, M. F. J. Exper. Med. **51**: 285, 1930

direct injury would result in an increased rate of filtration of the dye in the inflamed area and would account for the increased rate of fall in concentration of the dye within the capillaries Landis,¹⁹ however, recently demonstrated that when a wheal is formed on the skin by freezing or when a blister is caused by the application of cantharides plaster, the average capillary pressure at the point of injury rises appreciably This factor in addition to increased capillary permeability will also increase the filtration of substances into the extracapillary spaces

Further studies were then undertaken to see whether a metal would, like the dye, be fixed in situ by the inflammatory reaction²⁰ Iron was selected because of the ease of detecting this metal in tissues qualitatively by the prussian blue reaction When colloidal iron or ferric chloride is injected into the normal peritoneal cavity of rabbits, it rapidly accumulates in the retrosternal lymph nodes, as is shown by the prussian blue reaction, but it fails to reach these lymph nodes when it is injected into a peritoneal cavity in which inflammation has been caused either by aleuronat or by *Staphylococcus aureus* Quantitative studies by the method of Kennedy²¹ of the iron content of these lymph nodes in animals injected intraperitoneally with ferric chloride revealed 56.7 per cent more metal in the nodes of the animals with normal peritoneal cavity than in those with inflamed peritoneal cavity Experiments were then performed to demonstrate the accumulation of the metal in inflamed areas when ferric chloride was injected into the circulating blood stream Acute inflammatory reactions of from six to seven hours in duration were obtained by the injection of *Staphylococcus aureus* into the skin of the abdomen of rabbits Such acute inflamed dermal areas do not themselves give the prussian blue reaction, but when ferric chloride is injected intravenously the metal becomes demonstrable in these areas by the qualitative tests Quantitative determinations show, in inflamed areas of the skin of non-injected animals, as an average figure 9.7 mg of iron per hundred grams of dry tissue as compared with 16.2 mg in the inflamed areas of the skin of animals injected intravenously with ferric chloride, or an increase of 67 per cent in iron content after the introduction of the ferric salt The average iron content of normal areas of the skin in injected animals is 10.4 mg as compared with 8.4 mg in noninjected animals, showing an increase of 23.8 per cent as a result of injecting the metallic salt Thus about three times more metal accumulates in inflamed than in normal areas of the skin These observations show

19 Landis, E. M. Heart **15** 209, 1930

20 Menkin, V. J. Exper. Med **51** 879, 1930

21 Kennedy, R. P. J. Biol. Chem **74** 385, 1927

that iron, like trypan blue, accumulates in an inflamed area when injected intravenously and is fixed there by the inflammatory reaction

These studies may have clinical applications. It is conceivable that by the accumulation of dye, iron or other materials in an inflamed area, the character or course of development of the inflammatory reaction may be altered.

As previously mentioned, Opie¹³ showed that foreign protein injected into the skin of an actively immunized animal is fixed at the site of injection where the contact of antigen and antibody causes an acute inflammatory reaction (phenomenon of Arthus). In view of this work on immunized animals and of the results obtained with trypan blue and iron, experiments were undertaken to determine whether a readily identified foreign protein such as horse serum injected into an area of inflammation caused by either bacteria or a sterile irritant would also be retained in situ by the inflammatory reaction.²²

Horse serum was injected into the peritoneal cavity of normal rabbits and of rabbits that had previously been given an intraperitoneal injection of an inflammatory irritant. The presence of the foreign protein was tested by the precipitin reaction on blood samples removed at varying intervals from the heart. It was found that horse serum injected into an inflamed peritoneal cavity penetrates into the blood stream less rapidly than when introduced into the normal cavity. Furthermore, it was noted that when the foreign protein is injected into a cutaneous inflammatory area, it is held in situ for a longer period than when injected into an inflamed peritoneal cavity.

These experiments show that, like trypan blue and iron, complex foreign proteins such as are found in horse serum when injected into an inflamed area (caused in Opie's experiments by the contact of antigen and antibody and in the present experiments by a sterile irritant) are held fixed by the inflammatory reaction.

With the demonstration that the penetration of horse serum into the blood stream is delayed at the site of inflammation, the attempt was made to determine whether, as with trypan blue and ferric chloride previously studied, horse serum injected into the circulating blood stream would accumulate in inflamed areas to a greater extent than in normal tissue.

Areas of cutaneous inflammation were induced by the injection of about 0.2 cc of a saline suspension of *Staphylococcus aureus* into the skin of the abdomen of rabbits. About three hours later, 10 cc of horse serum was injected intravenously. The animal was killed when the inflammation was of from five to six hours' duration. Saline extracts obtained from the inflamed areas of the skin and normal

²² Menkin, V. J. Exper. Med. **52** 201, 1930.

areas of the skin were tested for the presence of horse serum. It was consistently found that a greater concentration of the foreign protein could be recovered from the site of inflammation than from the corresponding normal area of the skin. These results are, therefore, similar to those obtained with trypan blue and with ferric chloride. The accumulation of foreign protein in inflamed tissue is doubtless in part the result of the increased passage of fluid from the circulating blood stream, but the observations previously recorded indicate that its escape from the site of inflammation is retarded.

These observations offered a means of explaining an interesting observation made some years ago by Auer²³. This investigator showed that if the ear of a rabbit immunized with horse serum is painted with xylene following reinjection of the homologous antigen into the peritoneal cavity, an intense inflammatory reaction followed by necrosis takes place in the affected ear. No such severe reaction was seen when xylene had been applied to the ear of a normal rabbit after a single injection of horse serum.

In view of the observations on the accumulation of foreign protein in inflamed areas it is highly probable that the reaction in Auer's experiment is simply the result of an accumulation in the inflamed ear of sensitized animals of antigen and antibody from the circulating blood stream. The contact of antigen and antibody in the tissues evidently causes an acute inflammatory reaction, thus intensifying the mild reaction produced by xylene alone. This explanation was verified by the demonstration in several experiments that horse serum from the circulating blood accumulates in greater concentration in the inflamed than in the normal ear.

It is also possible that the phenomenon of focal reaction in tuberculosis may be explained by the foregoing observations. When tuberculin is introduced into the blood stream of an animal with a tuberculous lesion, an intense inflammatory reaction may develop in the lesion. The mechanism of this focal reaction in tuberculosis is not understood. It is conceivable in view of the experiments with horse serum that in a like manner tuberculo-protein from the blood stream may accumulate in the inflamed tuberculous lesion and by its presence there induce a local inflammatory reaction.

Some recent work by Schwartzman²⁴ described an interesting reaction that occurs when the filtrate of *B. typhosus* is injected into the skin of rabbits. If twenty-four hours later the same filtrate or a filtrate of a nonrelated organism such as the meningococcus is introduced into the blood stream, hemorrhagic necrosis often takes place at

23 Auer, J. J. Exper. Med. **32** 427, 1920.

24 Schwartzman, G. J. Exper. Med. **48** 247, 1928.

the site of the injection into the skin. The observations that I have presented on the accumulation and fixation of foreign proteins at the site of inflammation suggest that the intense reaction of the skin following the intravenous injection of bacterial filtrates may be the result of an accumulation of these substances in an area of skin already inflamed, with resulting accentuation of the original cutaneous lesion. The reaction does not necessarily have to take place with all bacterial filtrates or inflammatory irritants. Questions involving degree of capillary permeability and of optimum synergistic action of two irritating substances on one another may modify the final reaction. Conceived from this angle, it is suggested that the phenomenon may be purely a nonspecific reaction resulting from the accumulation of an irritating substance in an inflamed area. Frisch²⁵ recently demonstrated that this reaction took place in the prepared area of skin if the bacterial filtrate was injected intraperitoneally. When, however, the filtrate had previously been injected several times into the peritoneal cavity, the cutaneous reaction failed to occur when the filtrate was injected intraperitoneally, but not when it was injected intravenously. The failure of the reaction may perhaps be explained in terms of fixation of the bacterial filtrate in a peritoneal cavity inflamed by preliminary injections of the filtrate.

The studies on fixation have recently been extended to include bacteria and particulate matter.²⁶ The accumulation of bacteria at the site of inflammation from the circulating blood stream may explain the well known localization of bacteria in a locus minoris resistentiae in terms of increased capillary permeability with subsequent accumulation and fixation of bacteria at the point of injury.

After the demonstration that the accumulation of foreign substances from the circulating blood in an inflamed area is doubtless associated with increased capillary permeability, studies were extended in an attempt to determine the mechanism of fixation by the inflammatory reaction.²⁷

The leukocytes are probably not a very significant factor in the mechanism of fixation, for two reasons. Histologically, no definite evidence could be obtained of phagocytosed particles in the leukocytes of the inflamed area at a time when fixation of foreign substances was already demonstrable by examining the tributary lymphatics. In the second place, fixation of trypan blue at the site of inflammation was shown to occur as early as thirty minutes after the injection of the

25 Frisch, I. A. Demonstration of Local Immunity of the Peritoneum by Means of the Schwartzman Phenomenon, *Arch Int Med* **46** 410 (Sept.) 1930

26 Menkin, V. *J Exper Med* **53** 647, 1931

27 Menkin, V. *J Exper Med* **53** 171, 1931

inflammatory irritant¹⁶ The occurrence of fixation at this early stage of the inflammatory reaction, when there are as yet relatively few leukocytes present, seems to point toward some other factor responsible for fixation

A factor which may explain fixation is mechanical obstruction It is conceivable that a network of fibrin and thrombosed lymphatics at the site of inflammation may arrest the passage of particulate material injected into such an inflamed area The dissemination of fluids would probably also be retarded by mechanical obstruction of this kind, though probably not as effectively as solid particles which would be more readily caught in a fibrinous network In this connection it is interesting to note that some years ago Opie²⁸ showed that when cantharidin is administered intramuscularly the flow of lymph through the thoracic duct is at first diminished, but later may be increased The decrease in the flow of lymph was accompanied by acute edema of the liver and of the gallbladder This edema was due to plugging by fibrin of the afferent lymphatics and the sinuses of lymph nodes that drain these organs The observations of Adam² are also significant in this connection

Even when inflammation (as in pericarditis) affects the whole extent of a serous cavity, the layer of fibrin acts as a protective coat closing the lymphatic "stomata" hindering the free absorption of the morbid material by the lymph and blood vessels, and filtering bacteria out of such fluid as does find its way through to the tissues beneath

In the endeavor to throw some light on the mechanism involved in fixation, a series of experiments was undertaken to determine whether the inflammatory exudate in itself possessed some property that might facilitate the fixing of foreign substances in the inflamed area

It was found²⁷ that when ferric chloride was added directly to the inflammatory exudate, heavy precipitation occurred The compound formed is presumably a ferric proteinate²⁹ When horse serum was added to the exudate and incubated at 37 C for a short interval of time, coagulation occurred When, however, trypan blue was added to an inflammatory exudate, no effect was noticed Yet this vital dye was shown to be definitely held in situ by the inflammatory reaction The reaction of fixation must be due primarily to some other mechanism than precipitation or coagulation of foreign substances by the inflammatory exudate As it has been shown, however, that iron compounds are apparently more effectively held by the inflammatory reaction than trypan blue, it is possible that precipitation or coagulation of foreign substances acts as a secondary factor in the mechanism of fixation by preventing rapid dissemination from the site of inflammation

²⁸ Opie, E L J Exper Med **16** 831, 1912

²⁹ Smythe, C V, and Schmidt, C L A J Biol Chem **88** 241, 1930

Sections were made of the inflamed tissue of rabbits in experiments in which either trypan blue or ferric chloride had been shown to be fixed *in situ* by the inflammatory process. There is, as a rule, a central area of dense leukocytic infiltration. The intensity of the inflammatory reaction in the immediate neighborhood of veins and arteries is noteworthy. It is to be recalled¹⁶ that when the dye was injected intravenously it would not always penetrate into the central zone of the inflamed area. This is evidently due to thrombosis of the small vessels, for sections of such areas reveal some thrombosed vessels with acute inflammatory changes in the surrounding tissue.

Histologically, there is little evidence of phagocytosed particles of trypan blue or of iron within the leukocytes at a time when retention of these substances at the site of inflammation is clearly demonstrable.

It is of interest to note the meshwork of fibrin that is found usually at the periphery of the zone of dense infiltration (fig. 1). In the same region, careful study reveals many lymphatic vessels which are thrombosed, one of which is illustrated in figure 2. The thrombus is characterized by numerous leukocytes within a delicate fibrinous reticulum. The fact that there are many occluded lymphatics and a dense network of fibrinous strands within tissues that are distended with edema at the site of inflammation supports the view that foreign substances, especially solid particles, such as precipitated iron salts, can disseminate only with difficulty from the inflamed area through the regional lymphatic vessels.

If, as described, the thrombosed lymphatics and the network of fibrin in an acutely inflamed area are instrumental in preventing mechanically the free passage of substances from the site of inflammation, it follows that for the same reason similar substances injected at the periphery of the inflamed area should fail to enter it. To test this hypothesis, the following experiments were conducted at the suggestion of Professor Eugene L. Opie.

An inflammatory reaction was induced in the skin of the abdomen of a rabbit by the use of a bacterial irritant (*Staphylococcus aureus*) or by injecting concentrated broth. After a varying interval of time, trypan blue was injected at the periphery of the inflamed area in from four to six places. In this way the inflamed area became circumscribed by a blue band. In a normal area of skin, similar injections of dye were made to serve as control. Several hours later, the inflamed area within the original circumscribed blue band showed no trace of dye whereas the normal area of skin was diffusely blue. The dye had evidently failed to penetrate into the site of inflammation when injected at its periphery, owing to the presence of thrombosed lymphatics and of a fine network of fibrin in the tissue spaces. Experiments of the same type reproduced in frogs yielded similar results.

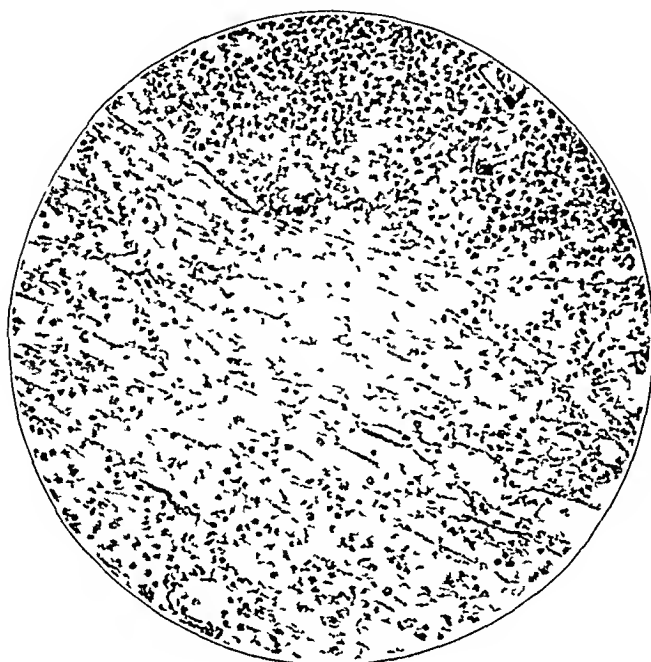


Fig 1—Site of inflammation, showing network of fibrin in the subcutaneous tissue of a rabbit. Trypan blue was injected directly into this area and was shown to be fixed in situ. Low power magnification. (From the *Journal of Experimental Medicine*)



Fig 2—Site of inflammation. Same section as in figure 1, but in a different field. A lymphatic occluded by a large thrombus. High dry magnification. (From the *Journal of Experimental Medicine*)

Direct observation with a binocular dissecting microscope demonstrated³⁰ that in frogs the failure of the dye to penetrate into an inflamed area was evidently due to the mechanical obstruction of lymphatic vessels by blood clots. These observations have recently been confirmed with bacteria.²⁶

Fixation of foreign substances by the inflammatory reaction is therefore primarily due to mechanical obstruction caused by a fine network of fibrin and by thrombosed lymphatics at the site of inflammation. Further experiments are being conducted to determine the relation between exudation from blood vessels and change in lymph flow from the site of inflammation. This phase of the problem still requires further investigation.

The reaction of fixation occurs extremely early in the inflammatory process. In some experiments,¹⁶ it was found that as short an interval as thirty minutes after the injection of an inflammatory irritant was sufficient to prevent the dissemination of a vital dye from the site of inflammation. This prompt and early reaction in the development of the inflammatory process circumscribes the irritating substance and allows a definite period of time for the leukocytes to assemble for the purpose of phagocytosis. Through this delicate nonspecific mechanism of fixation, the organism is protected at the expense of local injury.

30 Menkin, V. J. Exper. Med. **53** 179, 1931.

MECHANISM OF PRODUCTION OF SUBAURICULAR BEATS BY DIGITALIS BODIES *

HARRY GOLD, M D
ABRAHAM LIEBERSON, A B
AND
BEN GELFAND, M D
NEW YORK

While observing continuously the string of the electrocardiograph in an experiment on animals, after digitalis had been injected, we noted that a normal sinus rhythm was present when the animal was quiet, and that ventricular ectopic beats appeared temporarily after a struggle. This phenomenon recurred many times in the same animal. When the dose was increased, ectopic beats appeared and were uninfluenced by struggling. In another experiment, ectopic beats appeared spontaneously after an injection of digitalis and disappeared when the animal struggled. Struggling obviously calls forth a variety of agencies acting on the heart. Some of these agencies depend on the connection of the heart with the central nervous system, such as reflexes from various organs, others may produce their effects on the heart even after it has been isolated from the central nervous system, such as dynamic changes in the circulation or chemical factors in the blood, for example, epinephrine acting on the sympathetic nerve endings in the heart. The present investigation was undertaken to extend the preliminary observations and to study some of the factors involved in the production and abolition of ectopic beats by the struggling of an animal under the influence of digitalis.

REVIEW OF THE LITERATURE

Patients under the influence of digitalis may not show premature ventricular contractions during rest, but frequently they show a considerable number in the period of recovery after exercise. Spontaneous premature ventricular contractions in patients are known often to diminish in number or to disappear during exercise, only to reappear in greater numbers during the period of slowing of the sinus rate following exercise.

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* From the Department of Pharmacology of the Cornell University Medical College

In the course of an electrocardiographic investigation¹ of various digitalis bodies, a result was obtained in early experiments that seemed to be at variance with those obtained by other investigators. Robinson and Wilson² found that digitalis injected intravenously in several doses into the cat (10 per cent of the calculated fatal dose every ten minutes) called forth ventricular ectopic beats after the injection of approximately 70 per cent of the fatal dose. The percentages for the different animals of this group were fairly uniform, a very low figure being exceptional (70, 77, 72, 87.5, 78, 100, 28, 70, 71.5 and 64). With a specimen of tincture of digitalis which we employed in the same way, ectopic beats appeared much earlier in the first seven experiments, after about 45 per cent of the fatal dose had been administered, a very high figure being the exception in this series (44, 29, 90, 30, 42, 53 and 30). In a larger series of experiments with this specimen of the drug, some higher figures were obtained, so that in the entire group of sixteen experiments, ectopic beats appeared after an average of about 60 per cent of the fatal dose had been injected. There were two important differences between our experiments and those of Robinson and Wilson. First, we did not employ the same specimen of the drug. Second, they used ether anesthesia, and our experiments were performed without general anesthesia.

Halsey³ found that crystalline strophanthin injected intravenously into unanesthetized dogs frequently called forth ventricular ectopic beats after the administration of from 20 to 40 per cent of the fatal dose. Gold and Edwards⁴ observed that ectopic ventricular beats appeared only after 40 per cent or more of the fatal dose of ouabain had been injected intravenously into dogs anesthetized with ether.

All these observations have this factor in common, namely, that ectopic beats were produced with a smaller percentage of the fatal dose, in both dogs and cats, in those cases in which the animals were not anesthetized by ether during the course of the injections. This suggested that the ether might be the cause of the differences between the results obtained in unanesthetized animals and in those under ether anesthesia, since in the latter condition the animals cannot struggle, and reflexes are depressed.

It has long been known that the extrinsic cardiac nerves play an important part in the action of digitalis on the heart. Peacey and

1 Gold, H., Hitzig, W., Gelfand, B., and Glassman, H., *Am Heart J* **6** 237, 1930.

2 Robinson, G. C., and Wilson, F. N., *J Pharmacol & Exper Therap* **10** 491, 1918.

3 Halsey, J. T., *J Exper Med* **25** 729, 1917.

4 Gold, H., and Edwards, D. J., *Am Heart J* **3** 45, 1927.

Howard⁵ reported interesting experimental observations on the production of cardiac disturbances reflexly (elevation of the T-wave, decrease in the interval R to end of T and ventricular ectopic beats) in the dog under barbital anesthesia, by stimulation of various peritoneal viscera. They concluded from the experiments that the impulses passed over the sympathetic nerves (visceral afferent nerves to the cord and sympathetic efferent nerves to the heart) and that the vagi were not involved, because vagotomy did not influence the production of the disturbances. In some of these experiments it is probable that a relatively high degree of digitalization had been produced because enough of the drug had been injected at the start to call forth spontaneous ventricular ectopic beats. As we shall presently show, the vagal factor in the production of ectopic beats may be much more in evidence after smaller doses of digitalis. While it may be true that the reflex from the intestine to the heart is mediated directly through the sympathetics, it is probable that the vagus (efferent to the heart) could be shown to exert considerable influence on the production of ventricular ectopic beats through stimulation of abdominal viscera under certain conditions after smaller doses of digitalis.

The part played by the extrinsic cardiac nerves in the reaction of the heart to digitalis has been investigated experimentally in great detail by Rothberger and Winterberg⁶. They administered digitalis bodies to dogs and studied the effects of direct electrical stimulation and paralysis or excision of these nerves on the various cardiac structures. They showed that large doses of digitalis may call forth ventricular ectopic beats spontaneously but that after smaller doses, stimulation of the accelerator nerves may be necessary to produce them. In some cases in which both of these factors are insufficient, the additional stimulation of the vagus will produce them. Rothberger and Winterberg believed that sympathetic stimulation acts directly on the ventricle to increase its rhythmicity, already above normal as the result of the direct action of digitalis, while stimulation of the vagus produces no direct action but supplants a regular sinus rhythm by an idioventricular rhythm through suppression of the sinus pacemaker.

Robinson and Draper⁷ reported interesting observations on the production of a subauricular ectopic rhythm by the suppression of the sinus through vagal stimulation in children with organic heart disease in whom there was other evidence of high sympathetic tone.

5 Percy, J. F., and Howard, H. *Am Heart J* **2** 530, 1927.

6 Rothberger, C. J., and Winterberg, H. *Arch f d ges Physiol* **150** 217, 1913.

7 Robinson, G. C., and Draper, G. *J Exper Med* **15** 14, 1912.

DETAILS OF THE EXPERIMENTS

Experiments were performed on nineteen cats. The animal was tied on its back on the table. Since only minor operations were necessary, they were all performed with local anesthesia with phenol in oil. The excitement or struggling varied in intensity and in duration but was usually very brief. Sometimes it was spontaneous, at other times it was induced by pinching of the hind leg. The latter procedure did not produce any electrocardiographic changes unless struggling followed. Electrocardiograms were taken, lead II being used. In many cases, the tracing was started before and continued during and after the struggle, in order to record as accurately as possible the various time factors involved. In most cases, the sting was observed almost continuously throughout the course of the experiment. Three members of the digitalis group were used: a tincture of digitalis in seven experiments, digitoxin-Meick in six experiments and ouabain in six experiments. All injections were made intravenously in the dilutions described in the previous study¹. No qualitative differences between these substances were detected with reference to the phenomenon under investigation, hence, for convenience, we shall refer to the results in terms of digitalis alone.

In order to determine the part played by reflexes involving the nervous connection of the heart to the central nervous system, experiments were carried out in animals in which the heart was isolated by severing the vagi in the neck and removing the inferior cervical and stellate ganglions on both sides by dissecting in the neck along the course of the cervical sympathetic trunk. This operation was performed during ether anesthesia, the animal being allowed to recover from the anesthesia during a period of about two hours following the operation before the injection of digitalis was started. At this time, the animal was able to struggle violently, either spontaneously or after stimulation.

From eighteen to thirty-five electrocardiograms were obtained in each experiment. In the accompanying tables and figures typical records are reproduced, illustrating the conditions under which subauricular ectopic beats occur in the two stages in the action of digitalis. The P-P and R-R intervals were determined for the period of rest and at various times after the struggle. Since the record was often taken continuously before, during and after the struggle (in some cases it was necessary to discontinue during the most violent period of the struggle), it was possible to determine changes with considerable precision. No attempt was made to read the intervals to less than 0.01 second. Hence, when rates are referred to as being the same, it is possible that there were slight differences, which were not detectable by this technique.

In speaking of ectopic beats in this paper, only those of subauricular (usually ventricular) origin will be referred to. The intervals between subauricular ectopic beats will be designated r-r and those between normal beats, R-R intervals.

It is not feasible to present in detail the data of any number of the experiments. An intensive analysis of some of the electrocardio-

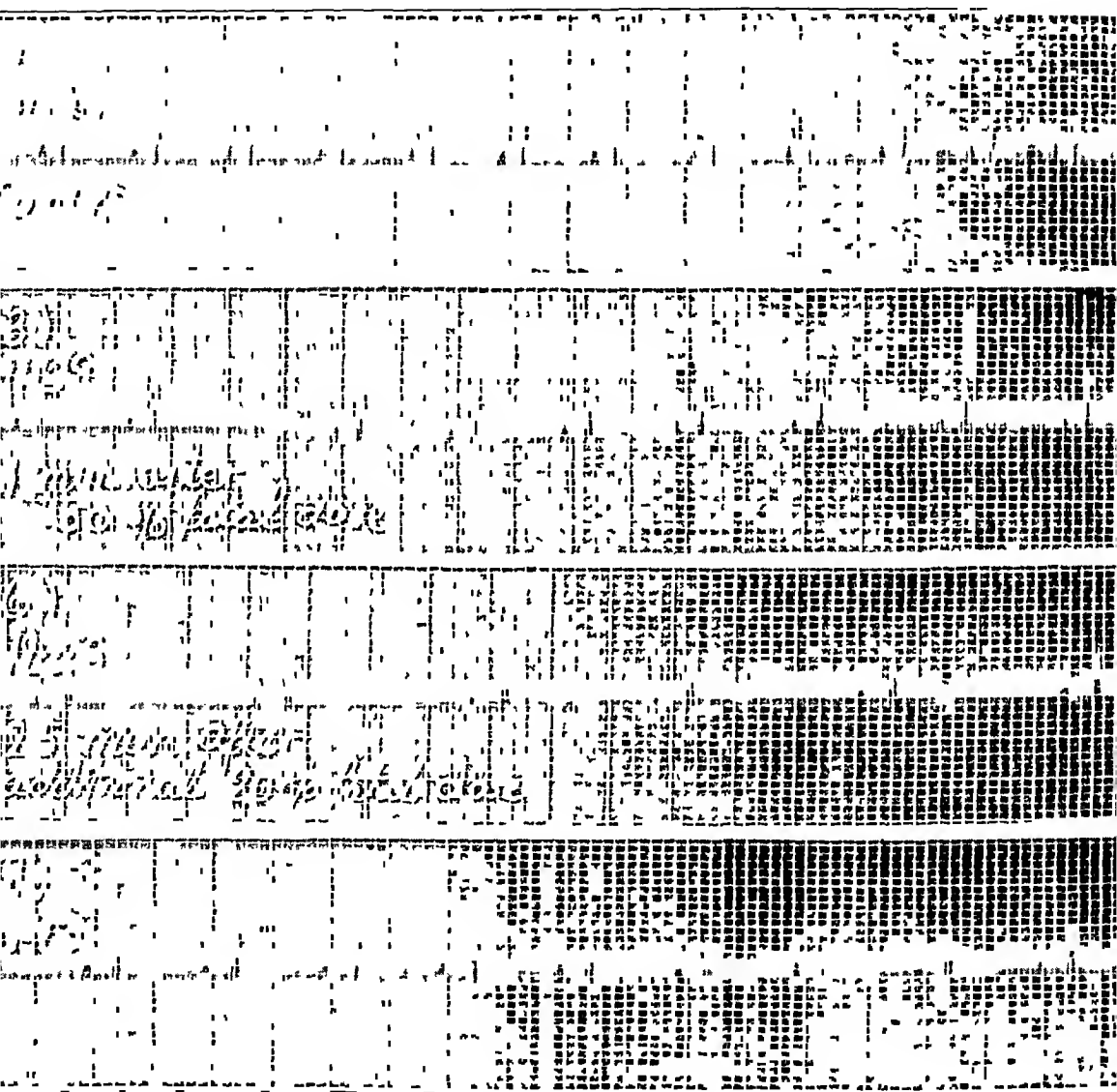


Chart 1—Marked slowing of the sinus rate after the administration of a small dose of digitalis. Struggling fails to produce ectopic beats.

grams obtained in one experiment is given to show the type of analysis carried out in all the others.

EXPERIMENT 1—Marked Slowing of the Sinus Rate, Struggle Fails to Produce Ectopic Beats—The electrocardiogram of the normal control (chart 1) showed a P-P interval of from 0.29 to 0.33 second and a P-R interval of 0.08 second. Fifty per cent of the average fatal dose of digitalis was injected, and

within one minute the P-P interval became from 0.41 to 0.48 second, the positive T-wave became negative and the P-R interval remained unchanged. After twenty minutes, 20 per cent more was injected, and the record eight minutes later showed a P-P interval of 0.72 second and a P-R interval of 0.11 second. This slow sinus rate did not persist long, as is shown in tracing 9. The record taken twenty-five minutes after the second injection is given in tracing 6. During this period the animal was made to struggle eight times, but no ectopic beats were produced.

TABLE 1—*Effect of a Struggle on the Production of Ectopic Beats Following the Smaller Dose of Digitalis**

Time of Recording	P-P Interval, Seconds	R-R Interval, Seconds
Immediately before struggle (condition of animal quiet)	0.32	0.32
After struggle	—	0.30
	—	0.34
One second after struggle	—	0.39 (R-r)
	—	0.36 (r-r)
	—	0.36 (r-r)
	—	0.34 (r-R)
	0.32	0.31
	0.34	0.36
	0.44 (P-p)	0.39 (R-t)
	0.36 (p-p)	0.37 (r-r)
	—	0.36 (r-r)
	—	0.37 (r-R)
	0.32	0.32
	0.33	0.32
	0.35	0.35
	0.40	0.39 (R-r)
	—	0.37 (r-r)
	—	0.38 (r-r)
	—	0.38 (r-r)
	—	0.39 (r-r)
	0.32	0.36 (r-R)
	0.32	0.32
	0.32	0.32
	0.32	0.32
	0.41	0.40 (R-r)
	0.34	0.36 (r-R)
	0.36	0.36
	0.34	0.35
	0.37	0.37
Tracing two seconds long omitted (no ectopic beats in this record)		
	0.33	0.33
	0.33	0.35
	0.36	0.36
	0.35	0.34
	0.38	0.38
	0.36	0.36
	0.34	0.34

* Tracing 16 of experiment 1, after the administration of 80 per cent of the average fatal dose of digitalis intravenously. r = ventricular or nodal ectopic beats, — = unable to read intervals with precision, p = inverted auricular deflection.

Ectopic Beats Produced by Struggle After Small Dose, Rate Slower Than That of Sinus Before Struggle—Eighty-two minutes after the second dose, a third injection of 10 per cent was made (total was 80 per cent of the average fatal dose in one hundred and two minutes). Three minutes later, struggling produced ventricular ectopic beats. During the subsequent period of two and three-quarter hours the string was watched continuously. It was noted that there was a normal sinus rhythm when the animal was quiet, and that the ventricular ectopic beats appeared temporarily after struggling. This effect of struggling was repeated eighteen times with only one failure during this period.

The conditions attending the production of ectopic beats by struggling after the administration of this dose of digitalis to this animal

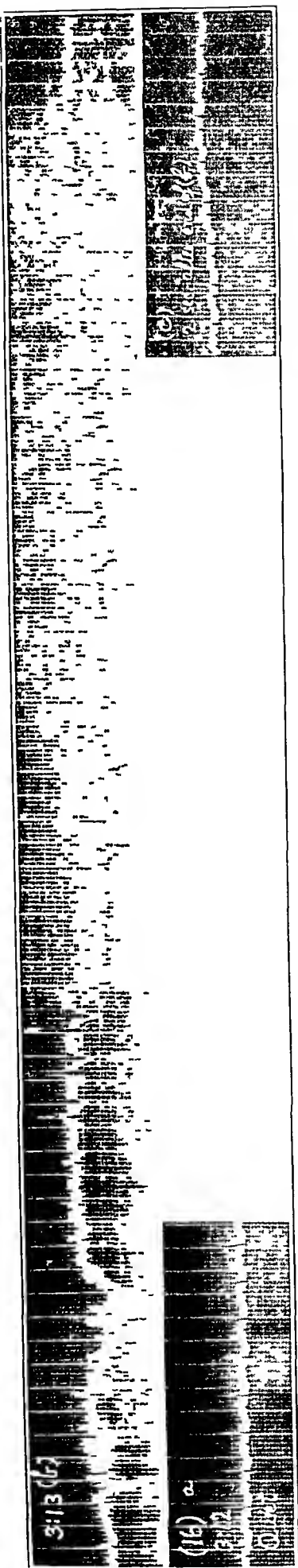


Chart 2—Ectopic beats produced by struggle after a small dose of digitalis, the rate being slower than that of the sinus before the struggle Note the effect of the exaggerated sinus arrhythmia

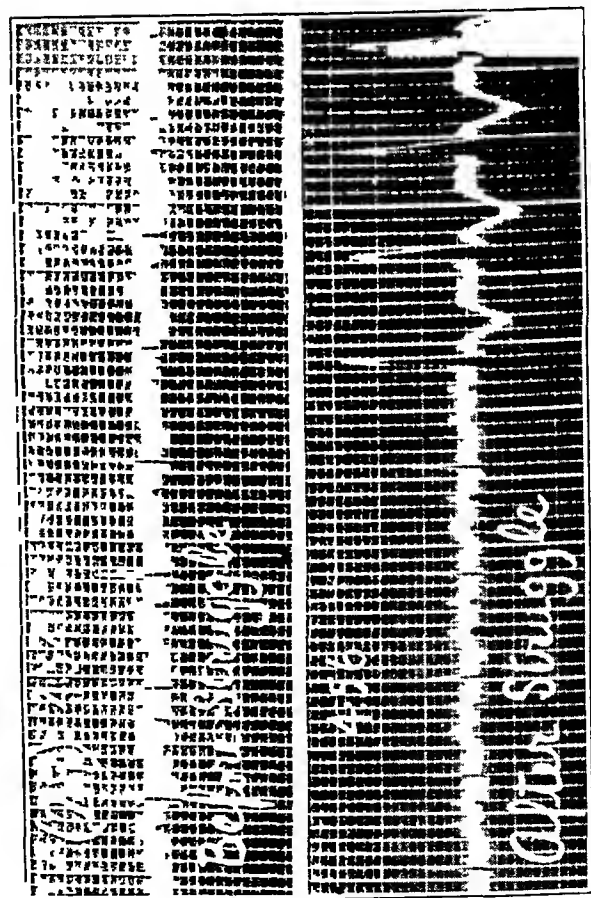


Chart 3—Ectopic beats produced by struggle after a larger dose of digitalis, the rate being slightly faster than that of the sinus before the struggle

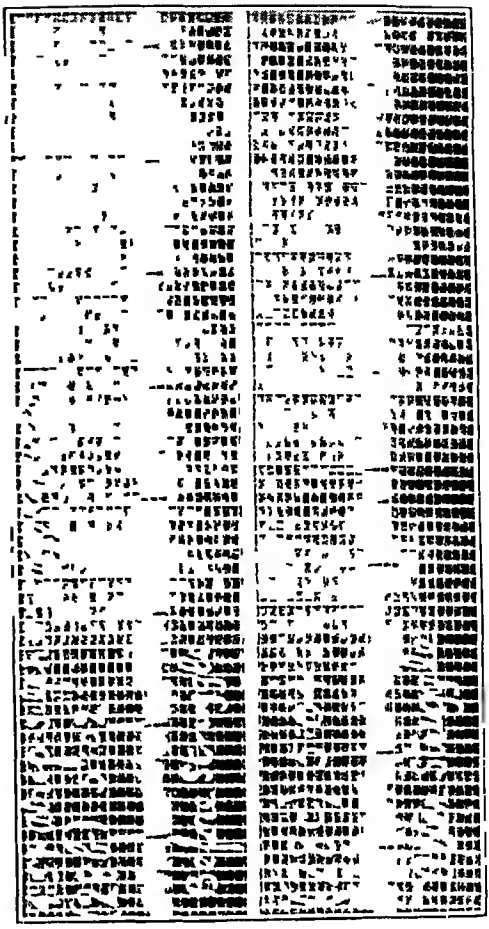


Chart 4—Struggle fails to produce ectopic beats after paralysis of the vagi

are illustrated in chart 2 and table 1. We refer to this period as the "vagal phase" of digitalis action (explained in the next section). Immediately before the struggling, a normal sinus rhythm was present with an R-R interval of 0.32 second. During the quiet period after the struggling, several periods of ectopic beats occurred, interrupted by short series of normal beats. The ectopic beats often occurred early in the cycle and their rate was slower than that of the sinus in the control, the r-r interval was 0.36 to 0.39 second. After the struggling a very marked and rapidly changing sinus arrhythmia was present, the P-P interval during the rapid phase being as low as 0.32 second and during the slow phase as high as 0.44 second. The ectopic beats were not present immediately following the struggle, but appeared after an interval of about one second. None of the four series of ectopic beats began during the period of the rapid sinus rate, they began only after the latter had slowed considerably below the resting rate of the control. Thus, while the R-R interval before struggling was 0.32 second, the interval lengthened in each case to 0.39 second or more before ectopic beats appeared. In the early part of the tracing, in which ectopic beats occurred, the P-P intervals varied between 0.32 and 0.44 second, and in the latter part, when ectopic beats were absent, the variations were much smaller, between 0.33 and 0.38 second. As the intensity of the sinus arrhythmia diminished, therefore, the ectopic beats disappeared. The rate of the ectopic beats was most rapid at first and then gradually became slower. Thus the r-r interval of the first series was 0.36, of the second series from 0.36 to 0.37 and of the third series from 0.37 to 0.39 second.

We have already noted that the interval between the R wave of the last normal beat and that of the first ectopic beat (the R-r interval) was constant, about 0.39 second in the record of table 1. However, this interval following a given dose of digitalis was not the same after different struggles, as one would expect, since it is obviously impossible to produce any two struggles of exactly the same intensity or duration. Table 2 shows some of these variations. The records of eight tracings are reproduced, taken from the same animal and after the injection of the same dose of the drug. These tracings are similar to those in chart 1, each having been taken after a period of struggling. Table 2 also shows that ectopic beats occurred only after marked slowing of the sinus rate and that the amount of slowing before the appearance of ectopic beats in the different tracings was not the same. In one instance, the ectopic beats appeared after a P-P interval of 0.38 second, while in another case, they were absent even after a P-P interval of 0.61 second. After a given struggle, however, the amount

of slowing in the sinus rate before ectopic beats occurred showed a certain type of constancy if more than one series of ectopic beats, interrupted by a series of normal beats, was present in the record. Thus in tracing 11 (table 2), each of the two series of ectopic beats began when the sinus rate had slowed to a P-P interval of 0.64 second; in tracing 12, the interval in each case was 0.47 second, and so on. This was, however, not absolutely constant (tracing 15, table 2). Furthermore, while a slowing to a P-P interval of 0.38 second was followed by ectopic beats in tracing 14 *d*, a greater slowing to 0.40 second in tracing 13 was not followed by ectopic beats. As far as

TABLE 2—*Variations in the Slowing of the Sinus Rate Before the Appearance of Ectopic Beats Following Struggles of Different Intensity and Duration*

Tracing	Longest P P Interval of Normal Rhythm, Seconds	P P Interval Between Last Normal and First Ventricular Ectopic Beat, Seconds	Series of Ectopic Beats in the Tracing
10	0.43	0.48	One
11	0.44 0.61	0.64 0.64	First Second
12	0.38 0.38 0.38	0.40 0.47 0.47	First Second Third
13	0.40		None
14-c	0.40	0.52	First
14 d	0.36 0.36 0.36	0.42 0.38 0.38	First Second Third
14-e	0.38 0.38	0.44 0.44	First Second
15	0.36 0.36 0.36 0.36 0.36 0.36 0.36	0.46 0.40 0.41 0.52 0.52 0.52 0.52	First Second Third Fourth Fifth Sixth Seventh

one could judge, the weakest struggle preceded tracing 13 and the strongest struggle in this period preceded tracing 14 *d*. It is therefore clear that if the slowing of the sinus rate following a struggle stands in any causal relation to the appearance of ectopic beats in the partially digitalized heart, it is not the only factor responsible for their appearance.

Ectopic Beats Produced by Struggle After Larger Dose, Rate Slightly Faster Than Sinus Rate Before Struggle—In three hours after the last dose of digitalis, struggling no longer called forth ectopic beats. Occasionally a single ectopic beat would appear after a struggle, there were six struggles in a period of seventeen minutes. We interpreted this result as due to the elimination of the rapidly eliminated fraction of digitalis, since sufficient time had elapsed for this to occur. An additional dose of 10 per cent was then injected, and two minutes later struggling was again effective in producing ectopic beats. The conditions attending the appearance of ectopic beats after this larger dose of digitalis are shown in

chart 3 and table 3 The P-P interval of the period before the struggle was practically the same as that after administration of the 80 per cent dose in table 1, namely, 0.32 second Again ectopic beats did not appear immediately, but began five seconds after the struggle and after the slowest sinus beat of the phase in which recovery takes place The first ectopic beat occurred early in the cycle, 0.02 second before the supraventricular beat was due, and at a time when the sinus rate had not decreased below that of the resting level, unlike that following the smaller dose of digitalis (table 1) Whereas the ectopic rhythm produced by struggling following the smaller dose was never faster than an r-r interval of 0.36 second, it was never slower than an r-r interval of 0.32 second after the larger dose of digitalis

Struggle Fails to Produce Ectopic Beats After Paralysis of Vagi—Fifteen minutes after the administration of the last dose of digitalis, the animal received atropine sulphate, 5 mg per kilogram injected intravenously, to paralyze the vagi Struggling seven times during the next forty-four minutes failed to produce ectopic beats A typical record obtained in this period is found in chart 4 The paralysis of the vagi did not accelerate the sinus rate appreciably, the P-P interval

TABLE 3—*Effect of a Struggle on the Production of Ectopic Beats After the Larger Dose of Digitalis**

Time of Recording	P P Interval, Seconds	R R Interval, Seconds
Immediately before struggle (condition of animal quiet)	0.32-0.34	0.33
After struggle	0.27 0.30 0.32	0.28 0.32 0.30 (R r)
Five seconds after struggle	r	0.32 (r r)

* Tracing 27 of experiment 1, after administration of 90 per cent of the average fatal dose of digitalis intravenously r = ventricular or nodal ectopic beats

before the injection of atropine was from 0.32 to 0.34 second, and five minutes after the injection it was from 0.32 to 0.33 second (compare 28 b of chart 4 with the tracing made before the struggle in chart 3) In the tracings after the struggle (28 c of chart 4) with the vagi paralyzed, no P-P interval was longer than 0.28 second This result was expected, since the slowing action of the vagi on the sinus had been excluded, and a slowing of the sinus then occurred only when the stimulation of the accelerator by the struggling began to subside

The part played by the vagi was also tested in other ways In one experiment in which struggling produced ectopic beats after an intravenous injection of 0.15 mg of digitoxin per kilogram, electrical stimulation of either vagus in the neck produced an ectopic rhythm In two other experiments in which the vagi were cut during the stage of the action of digitalis in which ectopic beats were produced by struggling, the latter phenomenon disappeared The exact interpretation of this result was not possible, because marked respiratory disturbances occurred in these instances, and when the trachea was opened to relieve the respiratory distress, marked acceleration of the heart occurred For these reasons atropine was used to exclude vagal action in most of the experiments

Struggle Again Produces Ectopic Beats After Additional Dose of Drug, Though Vagi Are Paralyzed—An additional 10 per cent of the average fatal dose of digitalis was injected twenty minutes after the injection of the atropine, and following a delay of about twenty-four minutes ectopic beats again appeared after struggling Struggling during this delay failed to produce ectopic beats The record obtained after paralysis of the vagi and after the administration of the

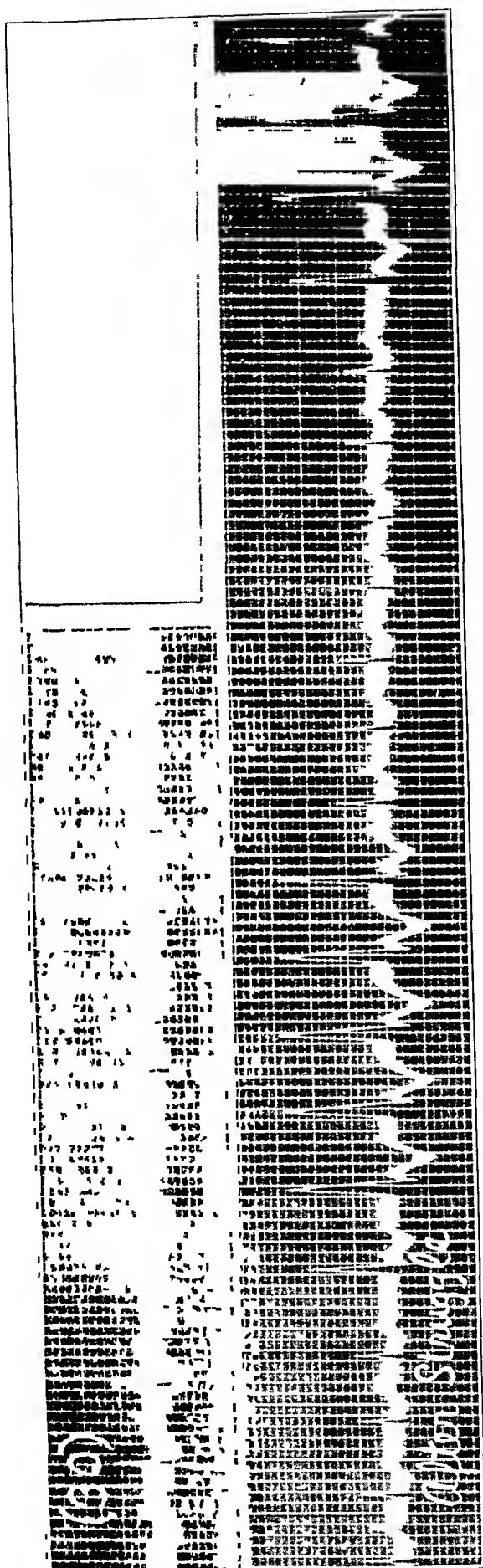


Chart 5—Ectopic beats produced, despite paralysis of the vagi, by struggle after the injection of an additional dose of digitalis

100 per cent dose of the drug is shown in chart 5 and table 4. While the sinus rate in the period of rest was not changed by paralysis of the vagi, the injection of an additional dose of digitalis increased the sinus rate of the animal while at rest from a P-P interval of 0.32 to one of from 0.29 to 0.30 second, and the P-R interval was increased from about 0.10 to 0.12 second.

In this record, the ventricular ectopic rhythm appeared following the struggle after the longest pause in the basic rhythm. The absence of definite P-waves after struggling suggests that the basic rhythm after struggling originated in the auriculoventricular node. The other possibility is that the basic rhythm was a sinus rhythm with a long P-R interval, the P-wave being superimposed on the T-wave.

TABLE 4—*Effect of a Struggle on the Production of Ectopic Beats After Paralysis of the Vagi by Atropine**

Time of Recording	P-P Interval, Seconds	R-R Interval, Seconds
Immediately before struggle (condition of animal quiet)	0.29-0.30	0.29-0.30
After struggle	—	0.25
	—	0.25
	—	0.27
	—	0.23
	—	0.32 (R-r)
Seventeen seconds after struggle	—	0.28 (r-r)

* Tracing 30 of experiment 1. — = intervals cannot be read, r = ventricular ectopic beats.

TABLE 5—*Intervals Between the Cessation of Struggling and the Appearance of Ectopic Beats with the Vagi Intact and After Paralysis of the Vagi by Atropine in Experiment 1*

Electrocardiogram	Vagi Intact, Seconds	Electrocardiogram	Vagi Paralyzed, Seconds
16	1.0	30 b	15
18 b	5.0	31-c	60
19 b	3.5	32-c	60
20 b	1.0	36 b	25
21 b	4.0		
21 d	4.0		
26 b	2.0		
27	5.0		

In the records made after the injection of the 80 per cent dose, the rate of the ectopic rhythm was slower than that of the sinus rhythm before the struggle, in those after the injection of the 90 per cent dose, the former was nearly equal to the latter, and those after the injection of the 100 per cent dose, the former was faster than the latter.

Paralysis of the Vagi Delays Appearance of Ectopic Beats—In this animal, therefore, with certain doses of digitalis, paralysis of the vagi prevented the production of ectopic beats by struggling. When the dose of digitalis was increased, ectopic beats again occurred, even in the absence of the vagal influence, but there was marked delay between the struggle and their appearance. This is shown in table 5.

Whereas they appeared in from one to five seconds when the vagi were intact, there was a delay of from fifteen to sixty seconds after the vagi were paralyzed

Since ectopic beats were produced by the larger doses of digitalis forty-four minutes after the administration of atropine, the possibility was considered that their reappearance might have been due to at least partial recovery of the vagi in this period of time, rather than to the additional quantity of digitalis acting in the absence of control of the vagus. That this was not the case, however, was shown by the fact that when the dose of atropine was repeated one hour after the first dose, it was entirely without influence on the phenomenon of the production of ectopic beats by struggling

COMMENT

In the course of the work we discovered that when digitalis is injected slowly intravenously (from 5 to 10 per cent of the average fatal dose at consecutive intervals of from five to ten minutes) the occurrence of subauricular ectopic beats can in most cases be divided into two stages in the order of the quantity of the drug required (1) the stage in which ectopic beats may be produced or abolished by struggling and (2) the stage in which the ectopic beat or rhythm occurs and remains uninfluenced by struggling. This was demonstrated in another way during the period of elimination of the drug. In several experiments the following phenomena were observed. A given dose of digitalis produced ectopic beats only after struggling, the dose was increased with the result that a spontaneous ectopic rhythm (without struggling) appeared, this persisted for varying periods of time (sometimes for days), after which the tracings for the control again showed a normal sinus rhythm with ectopic beats produced by struggling only, the latter, after varying periods of time (for several days in some experiments), was followed by a condition in which ectopic beats were absent in the resting period and could not be produced by struggling. The dosage necessary to produce the first stage varied from about 40 to 75 per cent of the average fatal dose. The percentage of the actual fatal dose for a given animal producing the various phenomena was not considered, because the total quantity was given in several doses. These experiments frequently lasted for many hours, hence, considerable elimination of previous doses took place.

We found, further, that both stages of action may be produced (a) in the intact animal, (b) after the vagi are severed in the neck or paralyzed by atropine, and (c) after double vagotomy in addition to the removal of both inferior cervical and stellate ganglions. An

analysis of the details of the results in relation to the doses of the drug revealed differences in the behavior of this phenomenon which show that while under certain conditions neither the vagi nor the stellate ganglions are essential, they may play an important rôle when they are intact

The individual experiments yielded results that are in many cases seemingly contradictory owing to the counterplay of several forces. These forces are at times difficult to follow, and it is hard to estimate the rôle played by each because they may all be brought into play at the same time, but most of the observations may be correlated if interpreted in the light of certain generally accepted views relating to the physiology of the heart and the action of digitalis. 1 The injection of digitalis directly increases the rhythmicity of the various cardiac structures capable of initiating impulses, the sinus, the auriculoventricular node, and the ventricle. 2 The center with the highest rhythmicity tends to become the pacemaker. 3 The vagus and sympathetic nerves act on some of these structures to change their rate and by stimulation serve to intensify the direct action of the drug, and the vagi do not alter ventricular rhythmicity directly, while sympathetic stimulation acts directly to increase it (Rothberger and Winterberg).

In experiment 1, while struggling produced ventricular ectopic beats, the appearance of the latter depended to a large extent on changes occurring in the recovery phase after the struggle (chart 2). Struggling depresses the vagi and stimulates the accelerator nerves. The sinus rate is increased as a result of a combination of these two actions in various proportions. The sinus acceleration alone tends to prevent the appearance of ventricular ectopic beats, while the simultaneous action of the accelerator nerves on the ventricle favors their production. For a short period after the struggling, vagal tone frequently increases beyond that of the rest period before the struggle. After the 80 per cent dose of digitalis in this experiment, the ventricular ectopic rhythm produced by struggling was slower than the sinus rate of the animal at rest, hence, the vagal factor in its production. For this reason, and for convenience of discussion we refer to this as the "vagal phase" of the action of digitalis. That this dose of the drug had increased the rhythmicity of the ventricle was seen from the fact that a struggle following a smaller dose failed to call forth ectopic beats, even though a greater amount of slowing of the sinus rate had occurred (chart 1). Thus far, only two factors could be detected, first, digitalis had increased the rhythmicity of the ventricle by a direct action, second, the vagal tone had been markedly increased above normal in the recovery phase after the struggle, thereby making the sinus pacemaker slower than the ventricle and allowing the latter to

obtain temporary control. As the vagus released the sinus during the period of exaggerated sinus arrhythmia, the ectopic rhythm disappeared.

Evidence that struggling also produced a direct change in the ventricle was obtained only after injection of the larger dose of the drug (90 per cent of the average fatal dose). In this case the rate of the ectopic rhythm induced by struggling was the same as, or slightly more rapid than, the sinus rate of the animal at rest (chart 3). Here then, it is apparent that the rhythmicity of the ventricle had increased as the result of the struggle, and in all probability due to stimulation by an accelerator. The effect was not seen immediately after the struggle because of the simultaneous acceleration of the sinus rate (above that of the ventricle). The effect of stimulation by an accelerator on the ventricle lasted longer, however, than that on the sinus, as one would expect, since the sinus recovers after struggling, not only by the disappearance of sympathetic action but by active return of vagal control. The term "accelerator phase" is used by us to indicate the period of action of digitalis in which struggling produces ventricular ectopic beats, the rate of which is the same as, or exceeds that of the sinus before the struggle.

Depending on a number of circumstances, the appearance of ectopic beats after struggling was either prevented, delayed or uninfluenced by paralysis of the vagi. With the smaller doses of the drug, in cases in which depression of the sinus was necessary before the latter became slower than the ventricle, the vagal factor was essential (chart 4). At this stage complete paralysis of the vagi prevented the heart from slowing sufficiently to produce ectopic beats after struggling. When the dose of the drug was increased, the accelerator factor excited by struggling became sufficient to produce ectopic beats even in the absence of vagal control (chart 5), but there was considerable delay in their appearance. This delay is caused by the simultaneous acceleration of the sinus, which takes longer to slow in the absence of the return of vagal tone. It is not possible to compare the actual intervals of time in one animal with those in another because of the marked variations. The rôle of the vagus in the delay is demonstrated, however, by the fact that in any single animal paralysis of the vagi under given conditions may delay the appearance of ectopic beats after struggling (table 5). The delay may conceivably last long enough to permit the recovery of the ventricle and thus prevent the appearance of ectopic beats after a struggle.

When still larger doses of digitalis were given to this animal, struggling produced ectopic beats with little or no delay even in the absence

of vagal control, because the rhythmicity of the ventricle in the period of rest was now so marked that the addition of the accelerator factor by struggling rendered the rate of the ventricle equal to or more rapid than that of the sinus. Under these circumstances, paralysis of the vagi proved to be without visible influence on the production of ectopic beats by struggling. This shows that the part played by the vagus and the sympathetic nerves is not a fixed one, and that with change in the conditions of the experiment very different results may be obtained, the rôle of these nerves may change from one in which they are essential to one in which they seem to play no part.

In this experiment, therefore, two distinct phases in the action of digitalis may be recognized: (1) the "vagal phase," in which an essential factor in the production of ectopic beats by struggling is the increased vagal tone after the struggle, and in which paralysis of the vagi may prevent the appearance of ectopic beats after a struggle, (2) the "accelerator phase," in which struggling produces ectopic beats even after paralysis of the vagi, though the severity of the struggle, the interval before the appearance of the ectopic beats or their duration may be modified. The former phase occurs after the relatively smaller doses of the drug, the latter after the larger ones.

Since the tone of the vagus varies greatly in different animals and may be absent in some, it is to be expected that in the animal in which the tone is low during the period of rest and in which little increase occurs after struggling, the vagal phase in the action of digitalis will be absent. An example of this was found in experiment 3. While 70 per cent of the average fatal dose of digitalis slowed the sinus rate from about 200 to about 84 beats per minute in experiment 1, the degree of slowing at all times in experiment 3 was negligible, from a rate of 200 to one of 190 beats per minute, and throughout the experiment the rate was generally above 200 beats per minute. Ectopic beats appeared later in the period of poisoning, only after 95 per cent of the average fatal dose had been injected in a period of sixty-nine minutes. At no time was the ectopic rhythm (induced by struggling) preceded by perceptible slowing of the sinus and the rate of the former was practically the same as, or faster than, that of the latter. In this animal the paralysis of the vagi by atropine was without influence on the production of ectopic beats by struggling.

Experiments 1 and 3 illustrate two extremes, namely, one in which the vagal phase is marked and one in which the vagal phase is absent. In the first, marked increase of vagal tone occurred almost uniformly after struggling, with the result that struggling in this phase of the action of digitalis failed to call forth ectopic beats only once out of eighteen trials in a period of two and three-quarter hours. In the

second, there was practically no increase of vagal tone, hence the vagal phase was entirely absent. In another experiment the increase of the vagal tone after struggling was extremely irregular (experiment 2) with the result that struggling frequently failed to produce ectopic beats in the vagal phase of the action of digitalis.

The vagal phase made itself evident in another way in experiment 4. Seventy per cent of the average fatal dose of digitalis caused marked slowing of the sinus rate in experiment 1, but no ectopic beats occurred. In experiment 4, 50 per cent of the average fatal dose caused less marked slowing of the sinus rate but at the same time so increased the rhythmicity of the ventricle that a ventricular ectopic rhythm appeared without any struggling. The sinus rate diminished from a P-P interval of from 0.30 to 0.34 second to one of 0.40 second and an ectopic rhythm appeared with an r-r interval of 0.38 second. Under these conditions, struggling by inhibiting the vagus and accelerating the sinus abolished the ectopic rhythm. The vagus remained in a state of partial inhibition during a considerable period of rest as seen from a rather rapid sinus rate (P-P interval 0.28 second). Ectopic beats were then produced during the period of increased vagal tone after a struggle (r-r interval 0.36 second). The importance of the vagal action was again seen when a spontaneous ectopic rhythm (r-r interval from 0.36 to 0.38 second) was reinduced by an additional dose of digitalis while the animal was quiet. This time vagal influence was removed, not by struggling, but by atropine. Atropine sulphate, 10 mg per kilogram, was injected intravenously and within one-half minute, a normal sinus rhythm was established with a P-P interval of from 0.28 to 0.30 second. During a period of eighteen minutes following the injection of atropine the animal was made to struggle seven times and no ectopic beats were produced, i.e., the addition of the accelerator factor by struggling in the absence of the vagal control was insufficient to produce an ectopic rhythm. When the dose of digitalis was further increased, struggling again produced ectopic beats, but with a rate much higher than in the early part of the experiment, the r-r intervals being from 0.24 to 0.26 second. In this experiment, therefore, struggling both abolished the spontaneous ectopic rhythm and induced an ectopic rhythm when it was absent during the control period.

Thus far we have seen that in a given animal the rate of the ectopic rhythm following a struggle was either the same, slower, or faster than the sinus rate when the animal was at rest after a given dose of digitalis. In experiment 15a, two phases of action were obtained after the same dose of the drug. Electrocardiogram 11 (chart 6) was taken after an intravenous injection of 0.15 mg of digitoxin-Merck per

kilogram The tracing was taken continuously before, during and after the struggle, and illustrative sections 1 to 7 are reproduced In the control period when the animal was at rest there was a marked sinus arrhythmia, the P-P interval varying from 0.30 to 0.37 second (section 1) This was abolished during the struggle, and immediately afterward the P-P interval was 0.24 second (section 2) The first ectopic beats appeared about thirty seconds after the struggling (sections 3 and 4), and their rate was faster than that of the sinus rate of the control (section 1), namely, r-r intervals of 0.28 and 0.30 second, respectively During the next thirty seconds eleven short periods

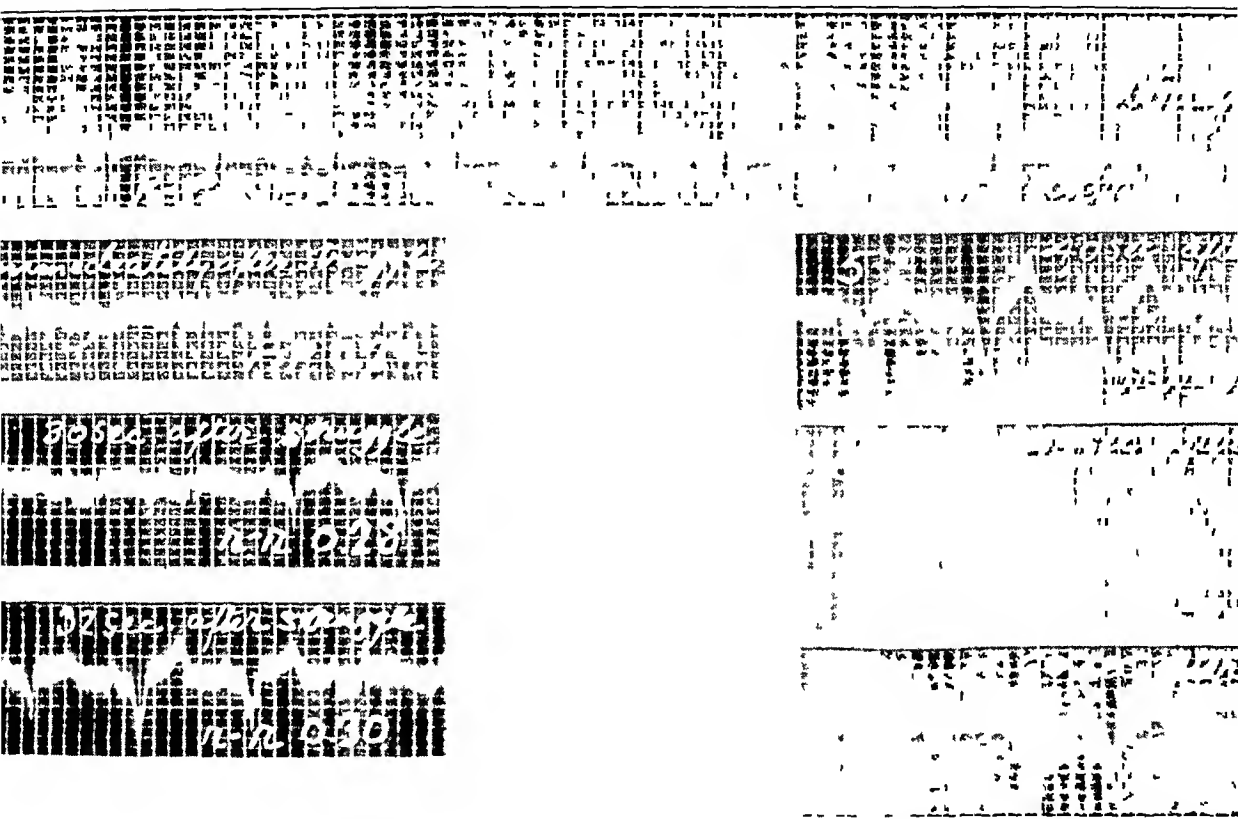


Chart 6—Electrocardiogram illustrating the occurrence of both the accelerator and vagal phases of the action of digitalis after a single struggle

of ectopic beats occurred, interrupted by periods of normal beats The rate of the ectopic beats in the successive periods became progressively slower until the last period, one minute after the struggle, when the ectopic rhythm was slower than the sinus rate of the control animal at rest, namely, an r-r interval of 0.40 second (tracing 7) The sinus rate was now also slower than at any time during the control period before the struggle, the P-P interval being 0.42 second

In this case the rhythmicity of the ventricle already increased by the direct action of the drug was further increased by the accelerator factor as the result of struggling to such an extent that an ectopic

rhythm appeared with a rate that was faster than that of the resting sinus. As the accelerator factor subsided in the succeeding period of rest, the rate of the ectopic beats diminished. When the ectopic beats became slower than the rate of the resting sinus, they continued to occur only because of the simultaneous increase in the intensity of the vagal action on the sinus. In this experiment the first groups of ectopic beats exhibited the accelerator phase of digitalis action, the later groups, the vagal phase.

ACTION OF DIGITALIS IN THE PARTIALLY DENERVATED HEART

The following are brief summaries of the three experiments in which the hearts were denervated.

EXPERIMENT 10—Heart Denervated, Difficult to Produce Ectopic Beats by Struggle—In this experiment the inferior cervical and the stellate ganglions were both removed during ether anesthesia, and after the animal recovered from the ether in a period of over two hours, the injection of ouabain was started. The heart rate in the absence of sympathetic innervation was slow when compared with that of the average unanesthetized cat tied down on the table, namely, an R-R interval of from 0.44 to 0.46 second. The P-waves varied from the positive through the intermediary stages to the negative sign, indicating in all probability a shifting of the pacemaker from the sinus to the auriculoventricular node. This shifting continued to occur during the administration of ouabain. After the vagi were severed there was severe struggling, and the heart rate increased to a P-P interval of from 0.37 to 0.38 second. The sinus then slowed to a P-P interval of from 0.41 to 0.42 second, thereafter only minor variations in the sinus rate were present during the resting period and struggling produced only slight acceleration (3 or 4 beats per minute).

Usually, the cutting of both vagi in the necks in cats results in respiratory disturbances due largely to closure of the larynx, necessitating tracheotomy. In this animal breathing became entirely normal after the initial struggle. Forty-seven minutes later the animal struggled violently and this was attended by what seemed to be respiratory difficulty, hence a tracheal cannula was inserted. The struggle may have induced a spasm of the laryngeal muscles.

After injection of 62 per cent of the average fatal dose of ouabain, a violent struggle called forth a ventricular ectopic rhythm in which the ectopic beats were coupled and the rate (r-r intervals of 0.32 and 0.42 second) was more rapid than the previous sinus rate by about 12 beats per minute. No rate for the animal at rest was obtained after the administration of this dose. The string was watched continuously, and ectopic beats were seen to appear just after spontaneous struggle. After the ectopic rhythm disappeared, further struggling failed to recall it.

The dose of ouabain was increased to 73 per cent, after which the resting sinus rate showed a P-P interval of from 0.39 to 0.40 second. Immediately after the animal struggled, the rate accelerated to a P-P interval of from 0.36 to 0.38 second (an increase of about 10 beats per minute), and every other beat was a ventricular premature contraction. When this rhythm disappeared, repeated struggling again failed to recall it. After the larger doses of ouabain, a slight struggle produced a ventricular ectopic rhythm the rate of which was more rapid, and the focus of which was frequently changed by struggling. This persisted

until the appearance of ventricular fibrillation. The rate of the ectopic rhythm was never faster than an r-r interval of 0.32 second.

EXPERIMENT 11—*Struggling Fails to Produce Ectopic Rhythm*—The heart was denervated in a manner similar to that in experiment 10. Double vagotomy performed after the excision of the inferior cervical and stellate ganglions was again without influence on respiration after a temporary disturbance. The heart rate of the animal while at rest was quite rapid (P-P interval from 0.30 to 0.31 second), and struggling resulted in practically no acceleration of the sinus (P-P interval from 0.29 to 0.32 second). It was found impossible to produce ectopic beats by struggling with any dose of ouabain. An ectopic rhythm appeared only after the fatal dose had been injected and persisted until death. This animal was more susceptible than the average, requiring only about 71 per cent of the average fatal dose to cause death. The heart continued to beat for about one minute after cessation of respiration, a condition that is not often seen in normal animals after a fatal dose of ouabain.

It is not possible to know what bearing the denervation had on the greater susceptibility and the cessation of respiration before the heart beat. Both phenomena are sometimes seen in normal cats, and both were absent in the other two animals with denervated hearts.

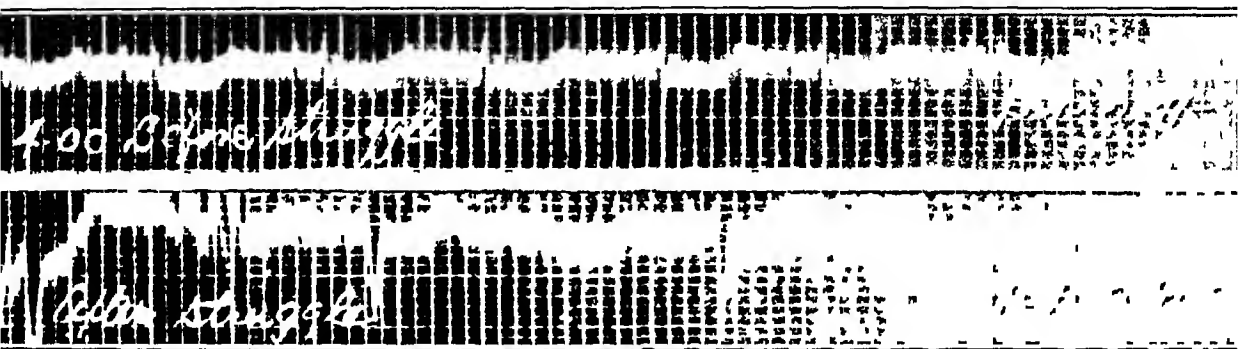


Chart 7—Ectopic beats produced by struggle in the denervated heart after the injection of ouabain. Note the absence of changes in the sinus rate.

EXPERIMENT 12—*Results Similar to Those of Experiment 3*—The same denervation was carried out. It was unnecessary to perform tracheotomy because after a temporary disturbance respiration was quite normal throughout. As in experiment 10, a spontaneous shifting of the pacemaker from the sinus to the auriculoventricular node and back to the sinus was seen in several tracings. The fatal dose of ouabain was practically the same as that for the normal cat, namely, 0.095 mg per kilogram. Struggling produced no acceleration of the sinus rate until 45 per cent of the average fatal dose had been injected, when the sinus rate increased from a P-P interval of 0.42 to one of 0.36 second after a struggle. The highest sinus rate was one with a P-P interval of 0.33 second while the animal was quiet following 53 per cent of the fatal dose. Struggling after the latter dose produced no acceleration of the sinus, in fact, there was a decrease in rate by 3 beats per minute. Tracings 11 a and 11 b of chart 7 serve to illustrate the conditions under which ectopic beats appeared. These were called forth by a struggle after 61 per cent of the fatal dose of ouabain. There was no acceleration of the sinus rate after the struggle, and no slowing of the sinus preceded the appearance of the ectopic beats. The cat reacted in a manner similar to that of the animal in experiment 3, when the dose was increased, a slight struggle called forth a ventricular ectopic rhythm, the rate of which, however, was slower than in the latter experiment, never exceeding an r-r interval of 0.36 second.

We have been referring to the stage in the action of digitalis in which struggling produces or abolishes subauricular ectopic beats as divided in a general way into the vagal phase and accelerator phase. This has been so expressed to signify that at a relatively early stage when the rhythmicity of the ventricle has not been greatly increased, the rate of the ventricular ectopic rhythm produced by struggling is usually slower than the rate of the sinus when the animal is at rest, hence the increased vagal tone is essential to its appearance, and that at a relatively later stage of action, the rate of the ventricular ectopic rhythm induced by struggling is equal to, or faster than, the resting rate of the sinus and action of the vagus is of little or no importance. The latter we have referred to as mediated through the sympathetic nerves, hence the accelerator phase.

In the matter of the part played by the vagus in the two phases of the action of digitalis there are some exceptions. Occasionally, slowing of the sinus rate below that of the control occurs after the vagi have been paralyzed. It is conceivable that the reaction of the vagal phase might occasionally be given by the denervated heart because, as Cannon and his associates⁸ have shown, the sinus rate in the latter is sometimes slowed after a struggle. Similarly, paralysis of the vagi may sometimes prevent the appearance of ectopic beats even in the accelerator phase, owing to the relatively excessive acceleration of the sinus rate by the struggling after the exclusion of vagal control over the sinus as seen in experiment 1 (chart 4).

Usually, however, paralysis of the vagi abolishes the phenomenon occurring in the vagal phase of the action of digitalis. It is now necessary to see what direct evidence may be adduced for the responsibility of the sympathetic nerves in the production of ectopic beats by struggling in the accelerator phase of the action of digitalis. If the sympathetic nerves are wholly responsible for the latter action, complete denervation of the heart should render it impossible to produce ventricular ectopic beats by struggling. If other factors are also involved (humoral or dynamic), complete denervation should simply modify the phenomenon. The results were quite variable in the experiments after double vagotomy and excision of both the inferior cervical and the stellate ganglions, in one, it was found impossible to induce ectopic beats by struggling, in another, the phenomenon was modified, losing the sensitiveness of a nervous reflex so that a violent struggle was necessary to produce ectopic beats, and repeated struggling failed to recall them, in the third case, the reaction was quite similar to that of the accelerator phase in a normal animal.

⁸ Cannon, W. B., Lewis, J. T. and Britton, S. W. *Am J Physiol* **77** 326, 1926.

We refer to the production of ectopic beats by struggling after double vagotomy and excision of both the inferior cervical and the stellate ganglions as the residual phase of the action of digitalis. That accelerator stimulation plays an important rôle in the accelerator phase is extremely probable, as seen from the observations of Rothberger and Winterberg⁶ by direct electrical stimulation of the stellate ganglions in digitalized dogs, as well as from the observations in our own experiments. But we have no data on which to base a statement as to the part played by other factors (humoral and dynamic) in this phase, and the part played by the accelerator nerves in the residual phase. This is due in the first instance to the difficulty of knowing when the heart is completely denervated. Cannon and his collaborators⁸ stated that the operation of double vagotomy and the removal of both stellate ganglions are equivalent in effect to complete denervation of the heart in acute experiments. They found that acceleration of the heart produced by struggling under these conditions was due to humoral factors (a secretion from the suprarenal glands and the liver). When the latter were excluded by excision of the gland or section of its nerve supply, struggling produced little or no acceleration of the heart rate. In survival experiments, after the foregoing operations, acceleration due to struggling again occurred which, it was found, resulted from the appearance of activity of sympathetic fibers to the heart from the thoracic chain frequently below the fourth segment. When the thoracic sympathetic nerves were also removed, acceleration from struggling was practically entirely abolished until regeneration of the paths (in thirty days or longer). These so-called completely denervated hearts still showed acceleration of from 4 to 14 beats (humoral factors have also been excluded) per minute when the animal struggled. Since our denervation experiments were acute, the view of Cannon and his co-workers would make it necessary to assume that in effect the heart was completely isolated from connection with the central nervous system, and further to assume that the residual phase is due to a humoral or dynamic rather than to a nervous factor. An objection to this assumption, however, arises from the possibility that the presence of a few sympathetic fibers might be insufficient to influence the sinus node, yet quite sufficient to affect the sensitized ventricle. Cannon and his collaborators⁸ used heart rate (presumably sinus rate) as the only criterion of cardiac innervation, and there is no evidence against the possibility that the sympathetic nerves might still be acting directly on the ventricle when there is no indication of a connection of the sinus with the central nervous system. At present, therefore, it is not possible to state whether the residual phase is due to humoral or

dynamic factors or to the activity of sympathetic fibers to the ventricle which give no evidence of their presence by the behavior of the sinus node. Further light will be thrown on this subject by more complete cardiac denervation and the exclusion of the glands of internal secretion.⁸

SUMMARY AND CONCLUSIONS

1 If an animal struggles while under the influence of digitalis, subauricular ectopic beats (ventricular or nodal) may be produced, abolished or left unaffected. The conditions that determine these different effects of struggling and the mechanism involved formed the subject of the present study.

2 Subauricular ectopic beats after the injection of digitalis occur in two stages, depending on the dose: (1) the stage in which they are called forth or abolished by struggling, and (2) the stage in which they appear spontaneously and remain uninfluenced by struggling (the focus may be changed by struggling in this stage).

3 The production or abolition of ectopic beats by the struggling of the digitalized animal does not depend on any single factor, but appears to be governed by the change in the relative rhythmicity of the sinus and the ventricle (or auriculoventricular node) resulting from the struggle.

4 The tendency to increased slowing of the sinus rate after struggling (below that of the sinus rate of the resting animal before the struggle) favors the production of ectopic beats. The slowing of the sinus rate is particularly necessary after the smaller doses of the drug when the rhythmicity of the lower centers is not very marked.

5 We have used the term "vagal phase" of digitalis action to designate that phase in which the rate of the ectopic beats produced by struggling is slower than the sinus rate before the struggle. The vagal phase occurs in animals with a very active vagal tone and after the relatively smaller doses of the drug. It is absent in animals with a low vagal tone. Paralysis of the vagi usually prevents struggling from producing ectopic beats in this phase of digitalis action.

6 In animals with a very active vagal tone, a relatively small dose of digitalis may call forth an ectopic rhythm which may then be abolished by struggling, owing to inhibition of the vagal influence on the sinus.

7 We have used the term "accelerator phase" of the action of digitalis to designate the phase in which the rate of the ectopic beats produced by struggling is equal to or faster than, the sinus rate before

the struggle. It occurs after the relatively larger doses of the drug. Paralysis of the vagi in the accelerator phase usually does not prevent the production of ectopic beats by struggling.

8. When the vagi and accelerator nerves are intact, they both play important though variable rôles in the production and abolition of ectopic beats by the struggling animal. Under certain conditions, however, struggling may produce ectopic beats in the digitalized animal after paralysis of the vagi and also after the removal of both the inferior cervical and the stellate ganglions in addition. The possible factors involved in this residual phase of digitalis action are discussed.

THE RELATION BETWEEN THE SO-CALLED RENAL LESIONS OF PLASMAPHERESIS IN DOGS AND CONTRACTED KIDNEYS IN MAN*

LOUIS LEITER, M D
CHICAGO

HISTORICAL REVIEW

From time to time reports have appeared in medical scientific literature describing experimental renal lesions supposed to resemble the characteristic morphologic processes of Bright's disease as it occurs in man. The variety of ways in which renal lesions have been produced is all the more remarkable since few of the methods employed in the experimental studies are in any manner effective in, or relevant to, the natural course of chronic diseases of the kidneys seen in man. A review of these procedures was published in 1924¹.

It was soon recognized by competent pathologists that there were at least two significant errors in the interpretation of the experimental nephropathies. In the first place, "spontaneous" disease of the kidneys in the particular animals employed was either entirely overlooked or inadequate allowance was made for them. In the second place, and this, unfortunately, seems to be a reflection on the investigator's knowledge of the details of the pathologic process of nephritis in human beings, the experimental renal lesions did not really resemble or duplicate, to any reasonable extent, the anatomic picture of chronic nephritis in human beings. In other words, "spontaneous" nephropathy occurs commonly in all sorts of animals used in the laboratory, but it is easily distinguished by a capable pathologist from the chronic nephritis of man. The frequently reported production of experimental chronic nephritis seems to simmer down to the periodic rediscovery, and possibly reproduction, of the "spontaneous" nephropathies. To this day no one has yet repeatedly produced a diffuse chronic nephritis—glomerulonephritis, more specifically—in any species of laboratory animal, and the picture of contracted kidneys such as occurs in chronic arteriolar sclerosis

* Submitted for publication, Nov 8, 1930

* From the Lasker Foundation for Medical Research and the Department of Medicine of the University of Chicago

1 Leiter, L. Experimental Chronic Glomerulonephritis, *Arch Int Med* **33** 611 (May) 1924

has not as yet been obtained. Such an accomplishment, however, would seem to be of the utmost importance in the understanding of Bright's disease.

The interesting feature of "spontaneous" nephropathies in various domestic animals is the relative uniformity of the pathologic process.

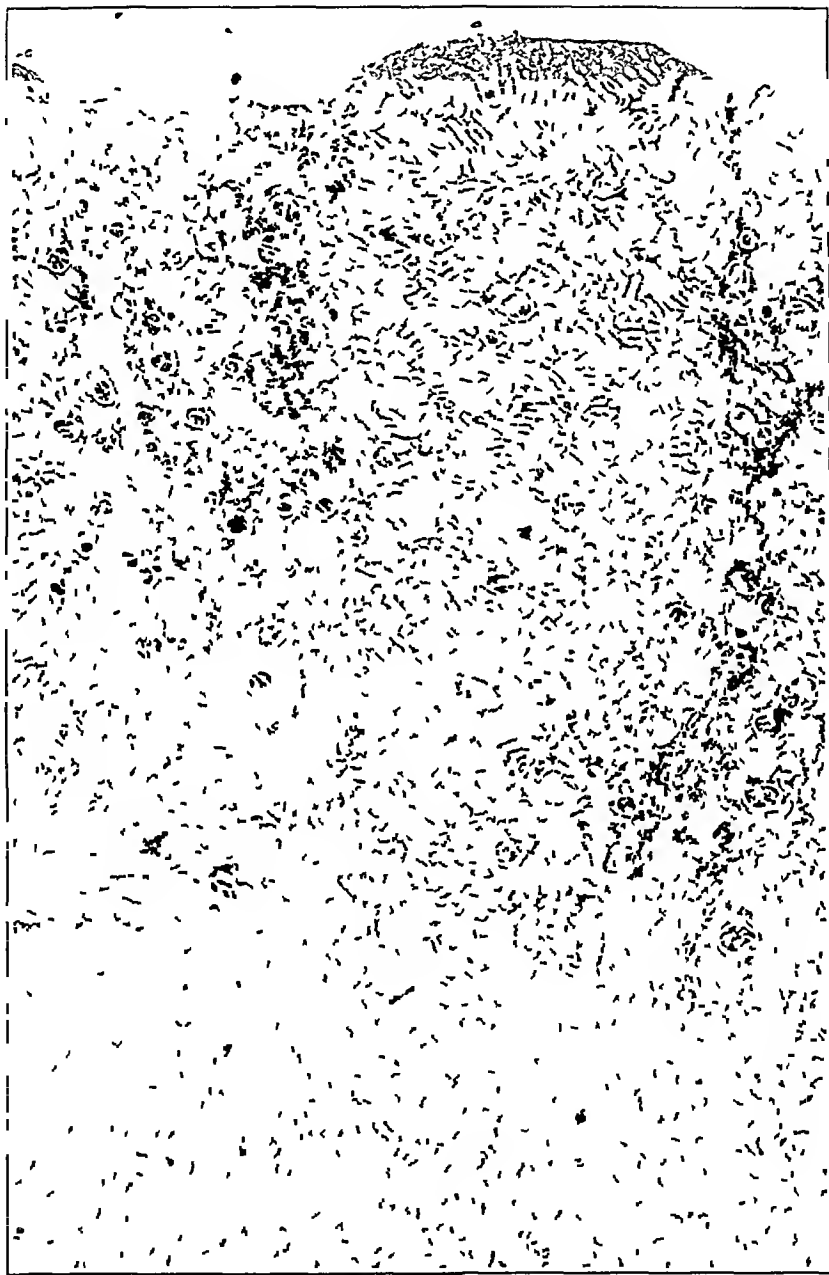


Fig 1 (dog 10) —Focal scars, causing a granular, pitted surface. Atrophic tubules, mononuclear cell infiltration and periglomerular fibrosis in these scars complete the picture of "spontaneous" interstitial nephritis. Reduced from a magnification of $\times 30$.

Whether one is dealing with the kidneys of the rabbit, the dog, the cat or the calf seems to make little difference. In all of these one is apt to find typical perivascular or interstitial foci of mononuclear cells,

with varying numbers of small lymphoid cells, eosinophils and other polymorphonuclears, distributed in varying degrees throughout the renal cortex. The foci are usually more marked near the boundary zone, but they often extend in linear fashion all the way up to the surface and some distance down into the medulla (figs 1, 2, 3 and 12). In such areas, if they are at all extensive, varying degrees of atrophy of compressed renal tubules may be seen. In advanced stages fibroblasts appear, and the originally heavily infiltrated regions become scars,



Fig 2 (dog 14) —Mononuclear cell infiltration and atrophy of the corresponding tubules, in the boundary zone. This represents an early stage in "spontaneous" interstitial nephritis. Reduced from a magnification of $\times 120$.

linear or wedge-shaped, radiating through the entire kidney and containing the debris of atrophied tubules and glomeruli with fairly normal tufts and concentric masses of connective tissue about the parietal layer of Bowman's capsules (figs 1, 4, 6, 9 and 11). Some of the tufts may be shrunken, occasionally they are adherent to their capsule, and they rarely undergo hyalinization. The fibrosis is usually most marked in the inner part of the cortex and the upper part of the medulla (figs 1, 5, 8 and 10). When this focal scarring is extreme, there may be a superficial resemblance to the contracted granular kidney

of chronic nephritis in man. However, there is always considerable normal renal parenchyma intervening between the scarred regions. Renal insufficiency is, therefore, only a remote possibility even in the contracted kidneys. The significant feature of the whole process is its predominantly interstitial character. The glomeruli and tubules are only involved secondarily, the blood vessels hardly at all. This, of course is radically different from the sequence of events in chronic nephritis in human beings. Excellent descriptions of the renal lesions

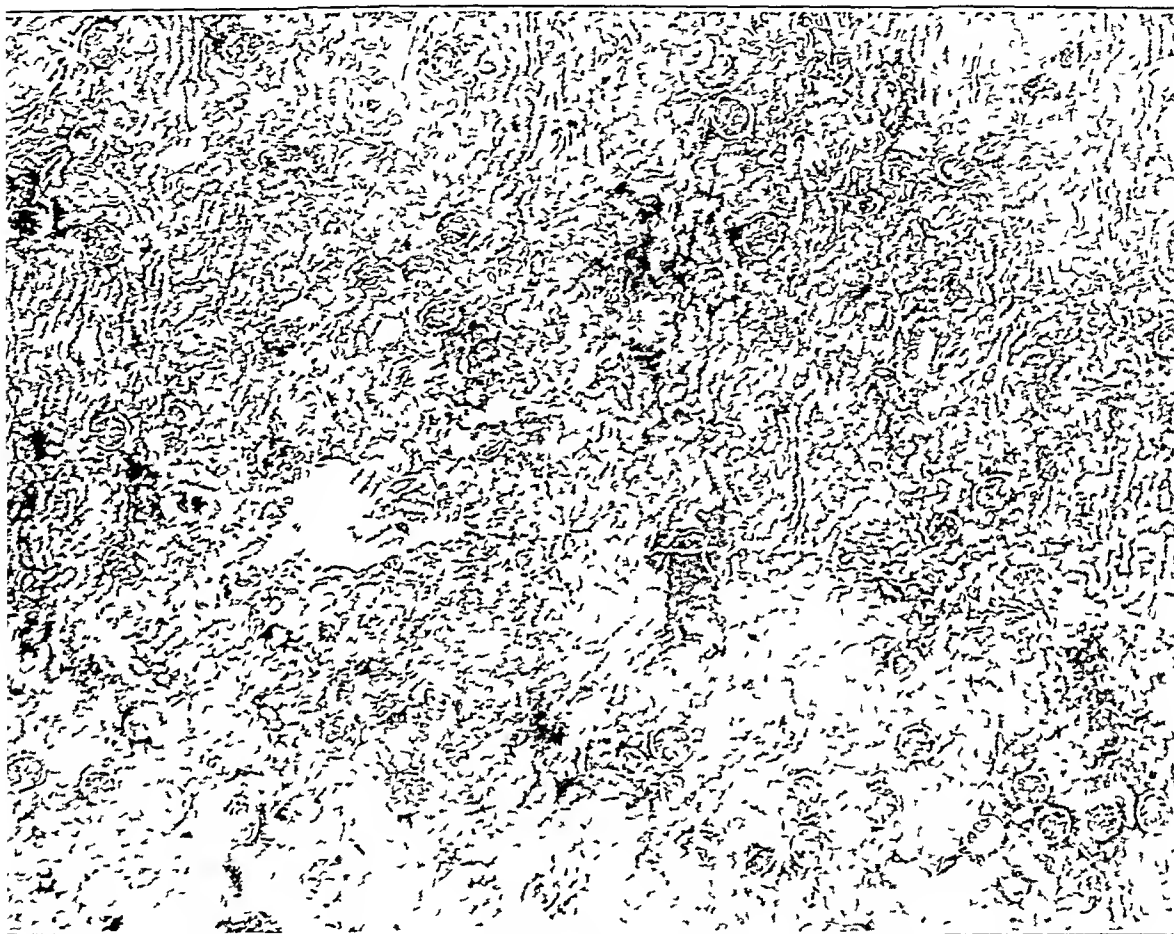


Fig 3 (dog 34)—Multiple foci of perivascular and periglomerular mononuclear cell infiltration in various levels of the renal cortex. Reduced from a magnification of $\times 33$.

in "spontaneous" nephritis have been published by Ophuls,² Dayton,³ LeCount and Jackson,⁴ MacNider,⁵ Bloomfield,⁶ Bell and Hartzell,⁷

2 Ophuls, W. J. M. Research **18**:497, 1908

3 Dayton, H. J. M. Research **31** 177, 1914

4 LeCount, E. R. and Jackson, L. J. Infect Dis **15** 389, 1914

5 MacNider, W. de B. J. M. Research **34** 177, 1916

6 Bloomfield, A. L. Bull. Johns Hopkins Hosp **30**:121, 1919

7 Bell, E. T. and Hartzell, T. B. J. Infect Dis **24** 618 and 628, 1919

Henschen,⁸ Roth and Bloss,⁹ Bell, Clawson and Hartzell,¹⁰ Smith,¹¹ Berger¹² and McFadyean¹³ Any one who attempts to interpret experimental chronic nephritis in laboratory animals might spare himself possible disillusionment and avoid drawing conclusions misleading to other workers in this field if he would carefully read these articles



Fig 4 (dog 33) —Typical linear area of mononuclear infiltration and beginning fibrosis Reduced from a magnification of $\times 95$

8 Henschen, F *Acta med Scandinav* **53** 774, 1921

9 Roth, W, and Bloss, K *Virchows Arch f path Anat* **238** 325, 1922

10 Bell, E T, Clawson, B J, and Hartzell, T B *Am J Path* **1** 247, 1925

11 Smith, T *J Exper Med* **41** 413, 1925

12 Berger, H *Berl tierarztl Wchnschr* **44** 613, 1928

13 McFadyean, J *J Comp Path & Therap* **42** 58, 141 and 231, 1929

The present publication has been stimulated by the recent papers of Barker and Kirk¹⁴ and Barker¹⁵ and the editorial comment¹⁶ connected with them. In view of the widespread interest in this subject, a detailed presentation of my own extensive work seems justified. In the course of several years of experience with plasmapheresis carried out on dogs, during which a nephrotic edema with a low protein content of the edema fluid was produced for the first time in dogs,¹⁷ a variety of renal

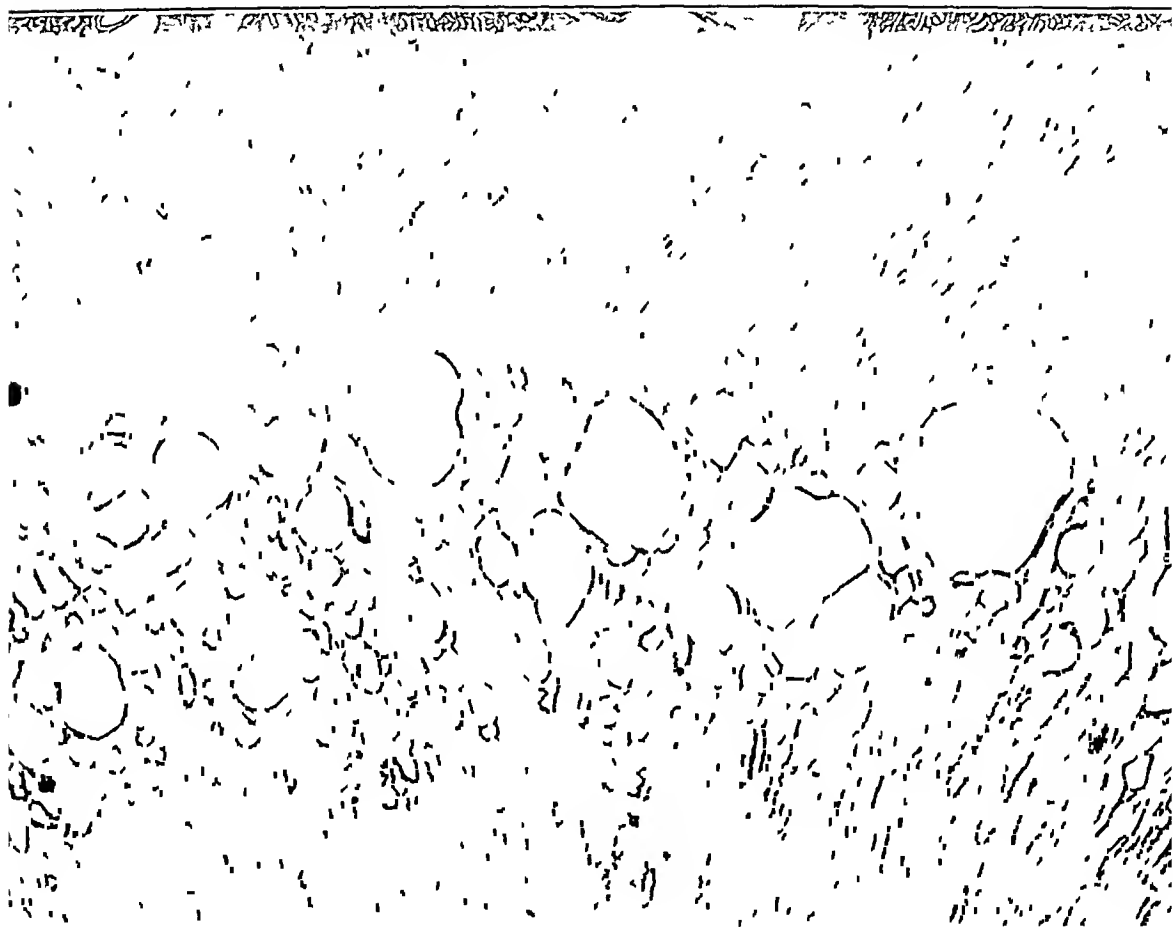


Fig 5 (dog 41) —Extreme dilatation of collecting tubules in the medulla with marked interstitial fibrosis throughout the boundary zone and the lower part of the medulla. Reduced from a magnification of $\times 17$.

lesions was encountered, most of which could be readily explained on obvious grounds and the rest of which were attributed to "spontaneous"

14 Barker, M. H., and Kirk, E. J. Experimental Edema (Nephrosis) in Dogs in Relation to Edema of Renal Origin in Patients, *Arch. Int. Med.* **45** 319 (March) 1930.

15 Barker, M. H. *Proc. Soc. Exper. Biol. & Med.* **27** 608, 1930.

16 Editorial, The Renal Lesions of Nephrosis, *J. A. M. A.* **94** 2066 (June 28) 1930.

17 Leiter, L. *Proc. Soc. Exper. Biol. & Med.* **26** 173, 1928, **27** 1002, 1930, Experimental Nephrotic Edema, *Arch. Int. Med.* **48** 1 (July) 1931.

nephropathy, with which a considerable familiarity had been acquired as a result of previous experience and a knowledge of the literature on this subject. It was, therefore, surprising to me that no mention of the possibility of "spontaneous" lesions was found in any of the published material previously mentioned. When the word "spontaneous" is used,



Fig 6 (dog 41) —Wedge-shaped scar in the cortex causing depression on the surface of the kidney. The usual features of "spontaneous" nephritis are clearly evident. Reduced from a magnification of $\times 90$.

it signifies the naturally occurring nephropathy of the characteristic type that develops independently of the experimental procedure, or renal lesions that are indistinguishable from the natural variety and that appear during the course of, and possibly in some way resulting from, the experimental technic.

It may be stated at once that the various stages of renal lesions described by Barker and Kirk¹⁴ and Barker¹⁵ fit in perfectly with the previously reported forms of "spontaneous" nephropathy in dogs. Cloudy swelling and hyaline droplet degeneration of the tubular epithelium are so common in toxic and infectious processes in the dog that they are of no significance. Fatty changes are to be interpreted in the light of Henschen's vast experience. This author⁸ stated that "the kidneys of dogs generally show a physiological fatty degeneration of

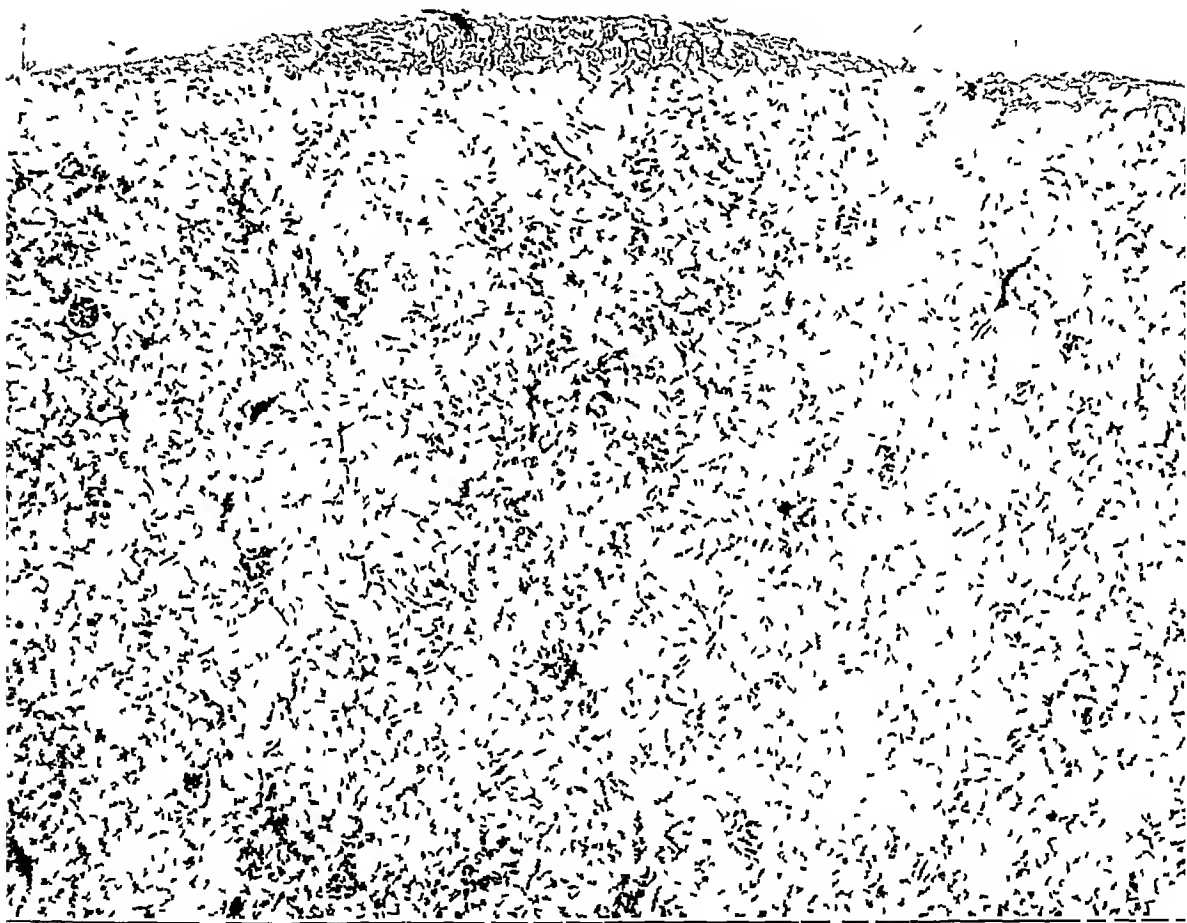


Fig 7 (dog 85) —Numerous areas of cortical fibrosis, tending to become confluent, without definite granulation of the surface of the kidney. This is an advanced form of chronic interstitial nephritis. Reduced from a magnification of $\times 35$.

the medullary tubules." The evidence consists of autopsies on 220 dogs. MacNider⁵ had previously come to an essentially similar conclusion. My own observations in a much smaller series led to the same interpretation. Barker and Kirk presented no satisfactory controls. In regard to their so-called secondarily contracted kidneys, representing, supposedly, the most extensive damage wrought by hypoproteinemia of long duration, Henschen⁸ must again be quoted. "Most of these renal atrophies, so usual in dogs, are due to acute interstitial, nonpurulent

nephritis" In other words, dogs have a truly interstitial chronic nephritis This is readily understood if one accepts Henschen's⁸ dictum that "acute interstitial lymphocytic nephritis is the most usual type of acute nephritis" in dogs, resembling the acute interstitial scarlatinal nephritis in man The "lymphocytes" are eventually replaced by fibroblasts, and focal scars are formed in which the remains of atrophic tubules and shrunken glomeruli may be discerned Bell, Clawson and Hartzell¹⁰ have more recently come to the same general conclusion concerning renal atrophy or contracted kidney in laboratory animals, they wrote

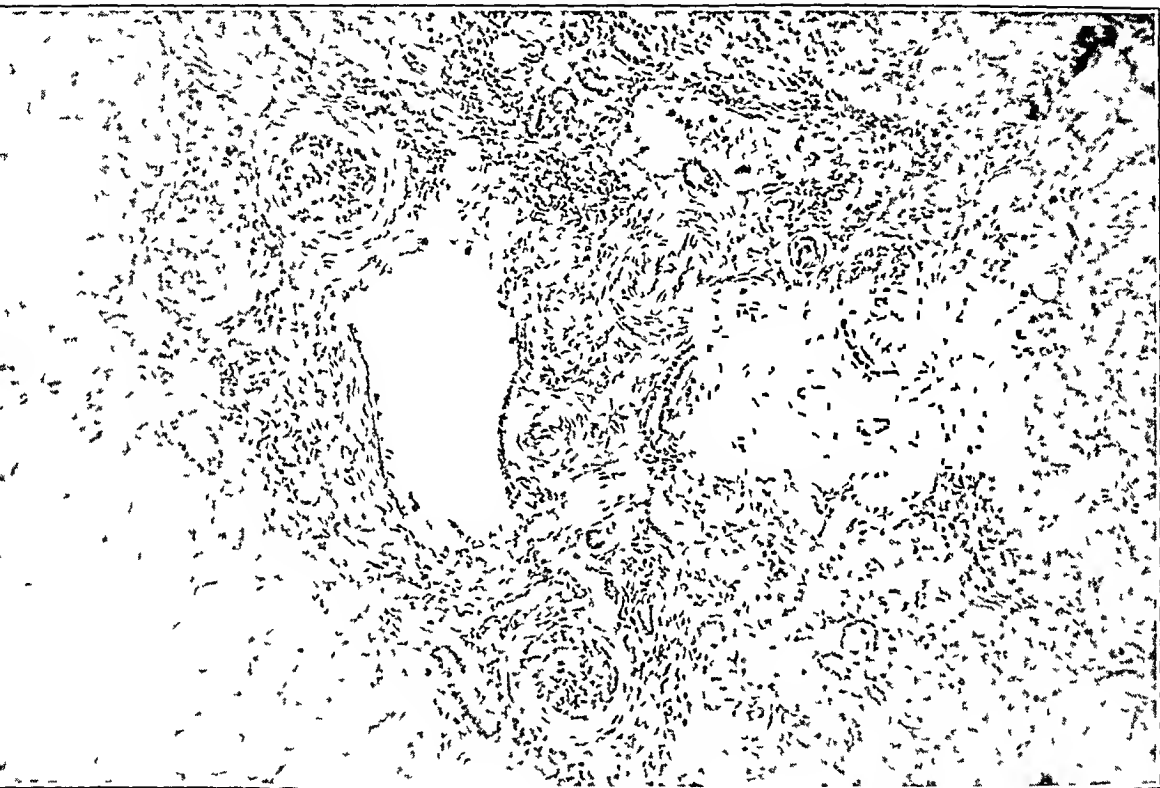


Fig 8 (dog 85) —Four glomeruli in the inner part of the cortex, to show the concentric fibrosis about Bowman's capsule The corresponding tubules are atrophic The arterioles are unaffected These lesions are probably "spontaneous" Reduced from a magnification of $\times 110$

that exudative interstitial nephritis caused "the only known form of contracted kidney" Their experience extended over many years In a comprehensive review of the pathology of nephritis in animals, McFadyean¹³ has emphasized the frequent occurrence of "chronic interstitial nephritis," or renal fibrosis, in dogs He gave excellently detailed descriptions of five instances and made the significant remark that "changes similar in nature and extent are not usually present in either of the forms of contracted kidney in man" The author's photomicrographs strongly support this opinion

EXPERIMENTAL WORK

Since Barker and Kirk¹⁴ have attributed the renal lesions of their dogs more or less directly to the hypoproteinemia, it would seem profitable to compare the type or stage of renal lesion in my dogs with the duration of the experiment. Approximately 100 dogs were used in this work and about 40 of them were bled sufficiently to reduce the plasma proteins to the level of edema. The accompanying table gives a summary of the essential data, and the photomicrographs illustrate the renal lesions observed. It is obvious that no particular relationship exists between the duration of hypoproteinemia and the degree of renal

Renal Lesions in Dogs with Hypoproteinemia

Dog	Days of Plasma- pheresis	Days of Experimental Life	Renal Lesions at Autopsy
72	3	3	Occasional area of mononuclear infiltration
85	3	4	Marked fibrosis of the cortex with tubular atrophy, acute focal hemorrhagic nephritis
14	5	5	Mononuclear infiltrates, infarct
32	5	5	Mononuclear infiltrates, infarcts
15	6	6	Perivascular mononuclear infiltrates
33	7	8	Slight mononuclear infiltration
92	8	14	Occasional linear cortical scar
10	9	10	Focal wedge shaped areas of granulation tissue in the cortex
11	9	10	None found
41	11	21	Wedge shaped cortical scarring, marked fibrosis and cystic dilatation of tubules in medulla
73	12	20	Occasional focal mononuclear infiltration or scarring, infarct and abscesses
70	15	18	Organizing small infarcts
71	15	28	Much perivascular mononuclear infiltration, infarcts and abscesses
17	18	31	None found
89	18	34	Linear areas of mononuclear infiltration, organizing infarcts
34	24	36	Marked mononuclear infiltration, infarcts
69	24	31	Medullary abscesses
35	29	47	Infarcts and abscesses
90	37	98	Organized infarcts
86	60	139	Moderate mononuclear infiltration, infarcts in process of organization, no other fibrosis

damage, if one considers fibrosis or scarring as the most advanced stage. The most extreme renal lesions were found in dog 85 (figs 7 to 9). In this dog, the kidneys showed little gross scarring or puckering, but there was microscopic evidence of a marked interstitial fibrosis, tubular atrophy and periglomerular fibrosis. This striking nephropathy was present in a dog that had had only three days of plasmapheresis, was then discarded and happened to die of distemper thirty-two days later. Incidentally, an acute focal hemorrhagic nephritis, probably related to the later distemper, was superimposed on the old process. The advanced renal lesions found in dog 41 (figs 5 and 6) can hardly be correlated with the brief period of plasmapheresis, and they are most likely "spontaneous" in origin.

It occurred to me that the repeated injection of erythrocytes suspended in a saline solution might be partly responsible for the so-called

renal lesions of plasmapheresis. The erythrocytes might clump together enough to embolize small renal arterioles and thus produce minute infarcts with secondary mononuclear infiltration and ultimate fibrosis. Barker and Kirk used aseptic technic throughout, so that experimental infection seemed to be ruled out as a factor in the interstitial nephritis of their dogs. On the other hand, I¹⁸ had not employed aseptic technic and I found the same type of renal lesions, in addition to ordinary infarcts and abscesses that could be attributed to emboli from cardiac

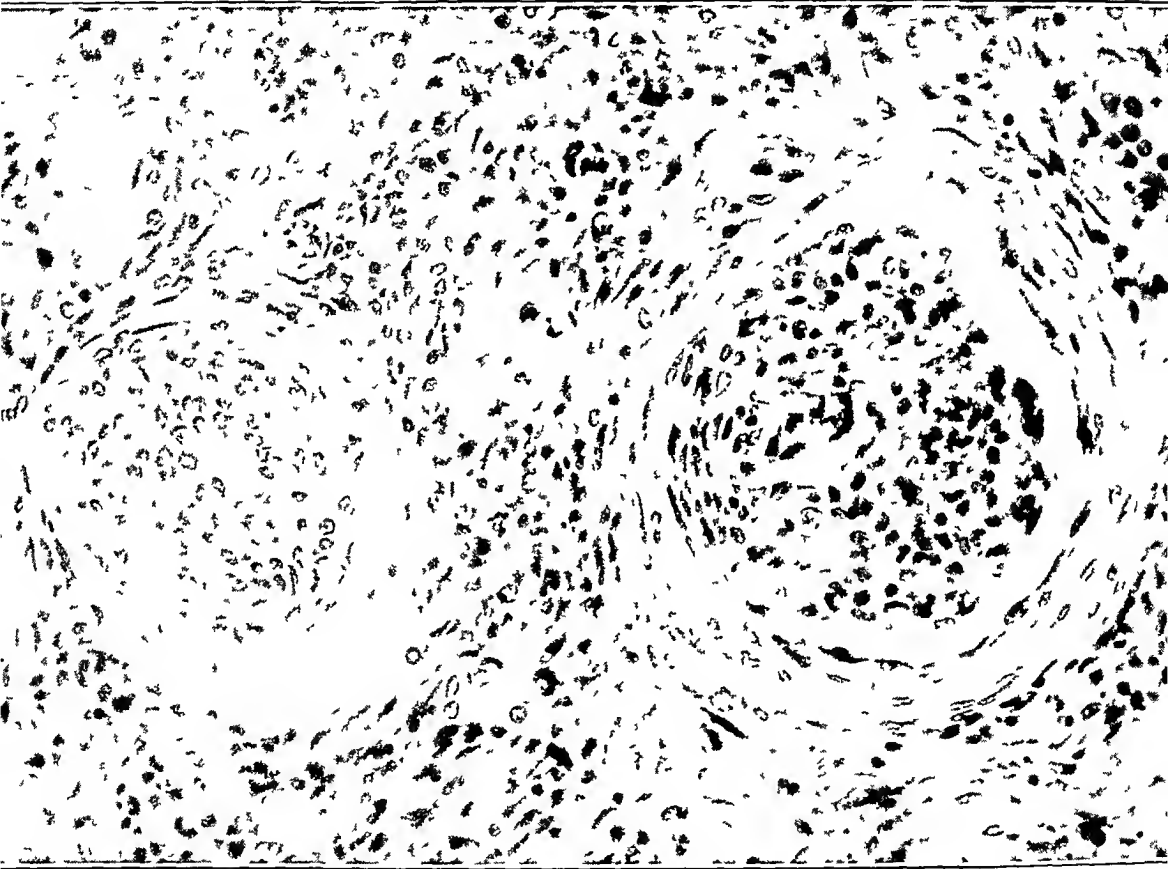


Fig 9 (dog 85) —Details of the two glomeruli in the upper right hand corner of figure 8. The shrinking of the tufts is secondary to the periglomerular fibrosis. Note the cellular infiltration and the degenerating tubules. Reduced from a magnification of $\times 400$.

vegetations of traumatic origin. In view of all this, a control series of dogs was given daily intravenous injections of from 200 to 400 cc of a suspension of donors' erythrocytes in a saline solution. Nothing else was done to these animals. Hypoproteinemia was absent. The results were interesting. Definite nephropathy was found in dog 39C, (fig 12), which had received transfusions of blood for twenty days

18 Leiter (footnote 17, third reference)

On the other hand, in dog 40C, which had been similarly treated for twenty-two days, the kidneys showed no changes. The ultimate outcome of such lesions is still undetermined, and it is even impossible to state whether or not the renal changes are the result of the experimental procedure.

By far the most extensive gross and microscopic renal lesions in this series of dogs were found in dog 16B, also a control animal. On each of two successive days this dog was given a transfusion of 500 cc of his own citrated whole blood, reinfected immediately after its withdrawal.

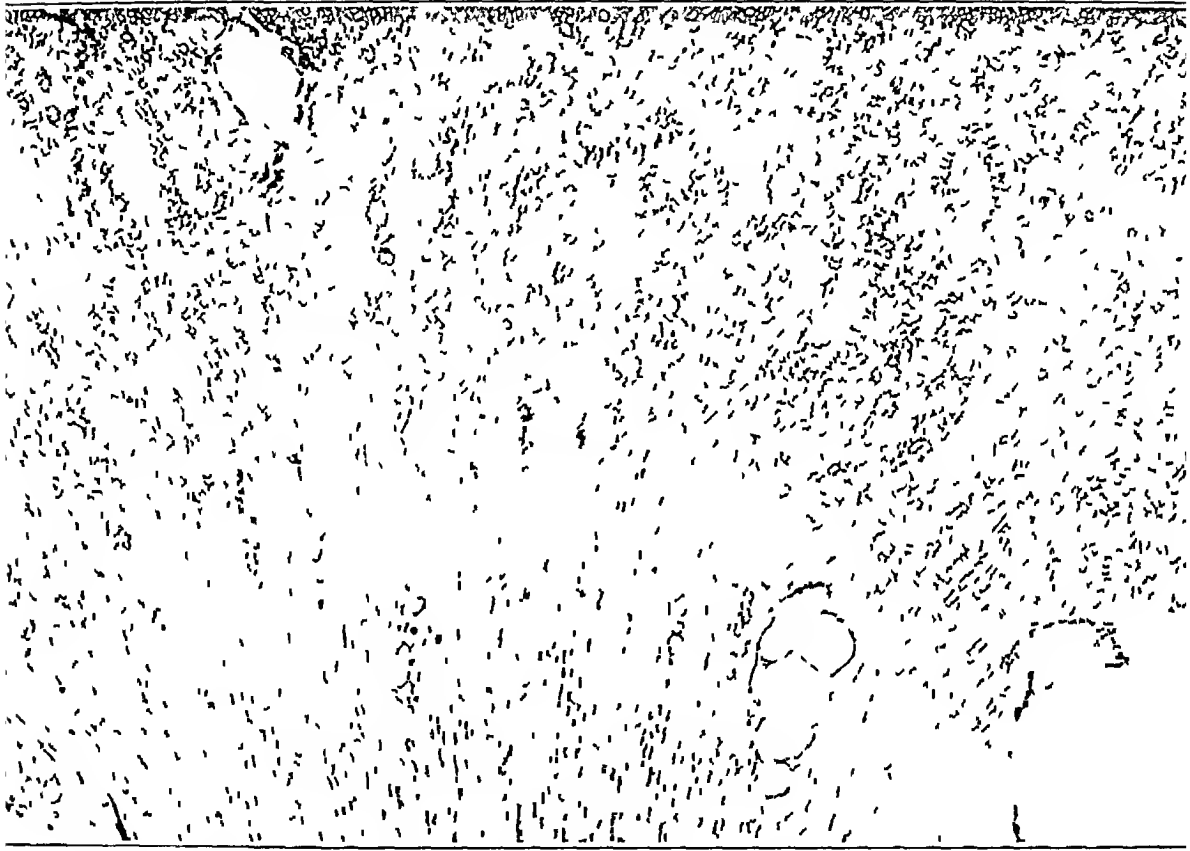


Fig 10 (dog 16B) —Extreme fibrosis of the inner part of the cortex and upper part of the medulla, in the form of linear scars radiating from the boundary zone. Reduced from a magnification of $\times 15$.

from the heart. The dog died on the second day, in shock. Examination at autopsy disclosed kidneys that were somewhat reduced in size, with partially adherent capsules and surfaces showing depressed irregular scars up to 3 mm in width, giving a roughly granular appearance. There was marked fibrosis of the inner part of the cortex and the upper part of the medulla, with some scars running all the way through to the depressions on the surface of the kidney. The microscopic features are shown in figures 10 and 11. The marked dilatation of some of the collecting tubules in the upper part of the medulla duplicates the condition described in some of McFadyean's¹³ dogs, it is best explained as

the result of obstruction by intertubular fibrosis (fig 5) Therefore, the advanced stages of the renal lesion described by Barker¹⁵ were found in a control dog of our series

From these results one may conclude that nothing definite can be concluded as to the actual etiology, or etiologies, of the renal lesions



Fig 11 (dog 16B) —Focal scar in the outer part of the cortex continuing on in the boundary zone and medulla Only the blood vessels are intact, while tubules and glomerular capsules have largely disappeared except for dilated remnants Reduced from a magnification of $\times 70$

in dogs during or following periods of plasmapheresis Above all, it must be emphasized again that the pathologic picture observed in the kidneys of dogs is entirely unrelated to that which one ordinarily finds

in chronic nephritis or "nephrosis" in human beings. As Bell and Hartzell⁷ suggested years ago in connection with similar lesions in the kidneys of rabbits, excretory pyelonephritis in man may be the analog of these renal lesions in laboratory animals. It may also be possible that those rare instances of chronic, truly interstitial nephritis in man,



Fig 12 (dog 39C) —Linear perivascular infiltrates in the inner part of the cortex, with more irregular subcapsular involvement. In these regions the tubules are disappearing by compression atrophy. Reduced from a magnification of $\times 28$.

supposed to result occasionally from acute interstitial nephritis, could be classed in the same group as the focal scarring of the kidneys of laboratory animals. Lowenthal¹⁹ recently reported a case of presumably

¹⁹ Lowenthal, K. *Ztschr f klin Med* **105** 420, 1927.

syphilitic, chronic, truly interstitial nephritis. Apart from such isolated rarities, there seems to be no connection between the renal lesions in dogs and chronic nephritis, or "nephrosis," in man. Hence Barker's¹⁵ statement that the secondary contracted kidney (in dogs) following a long-standing low proteinemia "would also suggest an explanation of why most so-called nephrosis cases that escape intercurrent infections die of uremia and at postmortem show scarred and contracted kidneys" has no foundation in fact. Similarly the editorial comment¹⁶ that a "secondarily contracted kidney may well follow a long-standing proteinemia as a result of tubular atrophy and scar tissue replacement" is equally without adequate experimental basis. The problem of the contraction of nephritic or "nephrotic" kidneys in man will be solved only when diffuse glomerulonephritis can be regularly produced in a laboratory animal. It will never be solved by speculation based on erroneous assumptions and uncritical experimental work.

CHEMISTRY AND METABOLISM IN EXPERIMENTAL YELLOW FEVER IN MACACUS RHESUS

IV TOLERANCE TESTS FOR DEXTROSE ¹

A MAURICE WAKEMAN, M D

AND

CLARE A MORRELL, M D

NEW YORK

A number of attempts to determine the impairment or loss of hepatic function by tests for dextrose tolerance have been reported in the literature Jacobsen,¹ Thannhauser and Pfitzer,² Hamman and Hirschman,³ Friedenson and his co-workers,⁴ and John,⁵ among others, have applied the test in several diseases by studying the blood sugar at stated intervals after the injection of dextrose or after feeding it by mouth. In many instances a lowered tolerance for sugar has been noted in diseases involving the liver.

In a previous paper,⁶ evidence was presented that indicated that in the extreme stages of yellow fever the liver is unable to maintain the blood sugar at its normal level, partly because of a diminished supply of hepatic glycogen. The unusually high level of blood sugar observed in a few moribund animals after meals further suggested that the ability to dispose of administered dextrose was impaired. To secure more direct information concerning this function, tests for sugar tolerance were carried out on *Macacus rhesus*.

* Submitted for publication, Nov 20, 1930

* From the laboratory of the West African Yellow Fever Commission of the International Health Division, Rockefeller Foundation, Lagos, Nigeria

1 Jacobsen, A T B Untersuchungen uber den Einfluss verschiedener Nahrungsmittel auf den Blutzucker bei normalen, zuckerkranken, und graviden Personen, *Biochem Ztschr* **56** 471, 1913

2 Thannhauser, S J, and Pfitzer, H Ueber experimentelle Hyperglykamie beim Menschen durch intravenose Zuckerinjektion, *Munchen med Wchnschr* **60** 2155, 1913

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A dose of 1 Gm of dextrose per kilogram of body weight was regularly used. Different methods of administering the dextrose were employed. In the case of twenty-three monkeys, of which thirteen were normal and ten infected with yellow fever, the sugar was given by stomach tube. In fifteen monkeys infected with yellow fever and fifteen normal monkeys, dextrose was given intravenously. In two cases a solution of dextrose was injected directly into the lumen of the small intestine.

In many instances bromsulphonphalein tests were carried out in conjunction with the tests for sugar tolerance.

The methods of taking samples of blood and of analysis have been described previously.⁶

The data presented here point to a lowered tolerance for sugar and support the hypothesis that in yellow fever the hepatic lesions render the animal unable to cope in a normal way with an influx of dextrose into the blood stream.

EXPERIMENTS

Blood Sugar Following Oral Administration of 1 Gm of Dextrose per Kilogram of Body Weight—Chart 1 presents representative curves for arterial and venous blood sugar for normal animals and for those ill with yellow fever. There is a great variability in the behavior of the normal animals. For example, in *M. rhesus* 11 the level of the blood sugar reached a maximum height thirty-seven minutes after dextrose was taken, and in fifty-two minutes declined below the fasting level, while in *M. rhesus* S1 the blood sugar had not reached a maximum one hundred and twenty minutes after the ingestion of dextrose. In *M. rhesus* 11 the greatest increase observed was only 22 mg per hundred cubic centimeters. Similar variations occurred in all of the normal animals studied. However, in all of the cases, the curves show that a definite hyperglycemia develops in which the concentrations of dextrose in the arterial blood exceed those in the venous blood.

While in the later stages of yellow fever, monkeys 12 and M40 were treated in a similar way. The distinct difference between the reaction of the sick monkeys and the normal ones to ingested dextrose is the obvious lack of rise in the blood sugar of the sick monkeys as compared with the definite increases in the normal animals. The flat appearance of the curves obtained from *M. rhesus* 12 and M40 may be due to lack of absorption or to rapid storage of sugar in yellow fever. The small arteriovenous differences observed would tend to discredit the latter view. That slow absorption is an important factor is shown by an experiment on *M. rhesus* 13 during the first day of fever. Two and one-fourth hours after the administration by stomach tube of 1 Gm of dextrose per kilogram, the blood sugar, which had not risen during

the interval, was still at fasting level. Five and one-half hours after the ingestion of dextrose, it had risen to 118 mg per hundred cubic centimeters from a fasting value of 92 mg per hundred cubic centimeters. An hour later, when the monkey was killed, of a total of 5 Gm, 2.5 Gm of dextrose was recovered from the stomach. The intestinal contents were not analyzed. There was no sugar in the urine. It is evident that after six and one-half hours, at least half of a small dose was not absorbed.

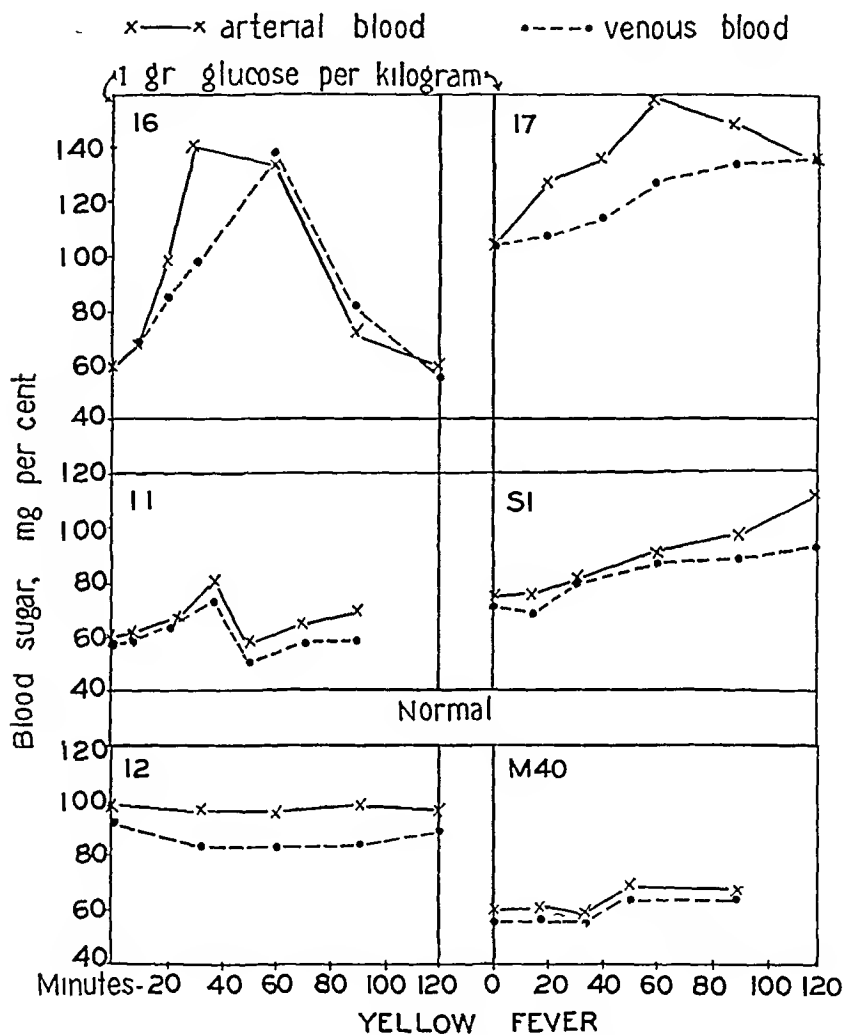


Chart 1—Curves showing arterial and venous blood sugar in normal monkeys compared with those of moribund monkeys with yellow fever, after the administration by stomach-tube of 1 Gm of dextrose per kilogram of body weight

Chart 2 gives the results of a series of tests for sugar tolerance made on different days of the disease

Macacus rhesus 14, a large female weighing 4.49 Kg, was inoculated on December 10 with 1 cc of blood from a case of yellow fever. On December 11, the temperature was 102.4 F at 9 a m, and 102.9 F at 5 p m. The animal was strong and fought vigorously. On December 12, the temperature was 105.1 F at 9 a m, and 104.9 F

at 5 p m The animal was still vigorous, but less active than on December 11 Urine collected after the experiment contained no sugar and 200 per cent of the bromsulphonphalein On December 13, the temperature was 103.3 F at 9 a m, and 101.3 F at 5 p m The monkey was weak but conscious At 5 p m, examination of the blood showed nonprotein nitrogen, 128 mg, urea nitrogen, 40 mg, and amino-acid nitrogen, 44 mg per hundred cubic centimeter On December 14 at 9.30 a m, the monkey died Ten cubic centimeters of urine from the bladder contained no sugar and 200 per cent of the bromsulphonphalein

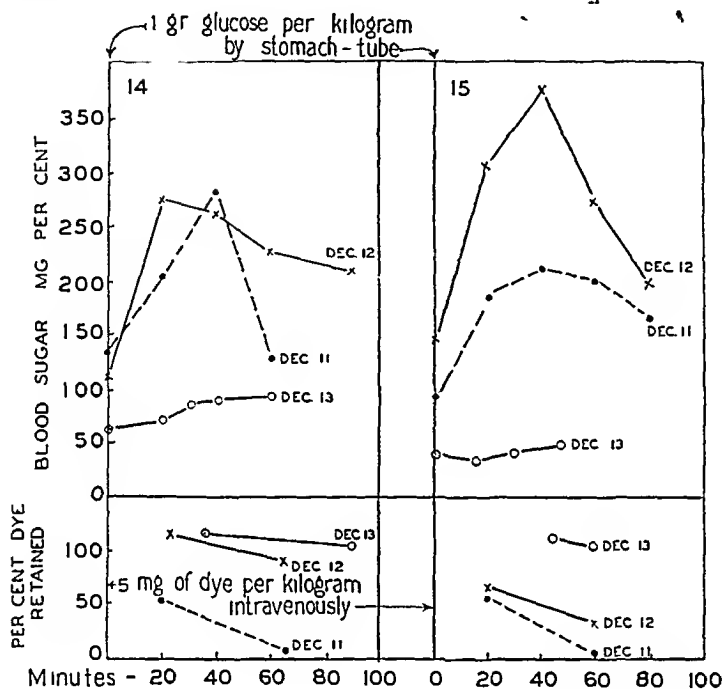


Chart 2—The changes in the curve for venous sugar of monkeys in the course of yellow fever. In every instance, 1 Gm of dextrose per kilogram was given by stomach-tube. Curves showing the retention of bromsulphonphalein are presented below for comparison.

Macacus rhesus 15, a large male, weighing 3.88 Kg, was inoculated on December 10 with 0.5 cc of blood infected with yellow fever. On December 11, it had a temperature of 103.5 F at 9 a m and 103.2 F at 5 p m. It struggled vigorously when handled. On December 12, the temperature was 104 F at 9 a m, and 104.7 F at 5 p m. The urine collected after the experiment contained no sugar and 20 per cent of the bromsulphonphalein. The animal feebly resisted handling. On December 13, the temperature was 100 F at 9 a m. At 11 a m, the monkey was moribund, unconscious and prostrate. It died at 12.37 p m. Three drops of the urine obtained from the bladder at autopsy contained no bromsulphonphalein. At

12 30 p m, examination of the blood showed nonprotein nitrogen, 91 mg, urea nitrogen, 25 mg, and amino-acid nitrogen, 33 mg per hundred cubic centimeters

One gram of dextrose per kilogram of body weight in a 6 per cent solution was administered to the monkeys by stomach-tube each day. A few minutes after ingestion, 5 mg of bromsulphonphalein dye per kilogram was injected intravenously. The curves shown in chart 2 represent the response of the venous blood sugar and the retention of dye in the blood on three successive days. *M rhesus* 14 retained more of the dye on all three days than did *M rhesus* 15. This is reflected in the larger excretion in the urine of *M rhesus* 15. The determination of dye in the urine was carried out by alkalinizing the undiluted urine and comparing it with the blood standard. For convenience, the concentration of dye was expressed in the same terms as that in the blood.

The increase in blood sugar on December 11 in both *M rhesus* 14 and *M rhesus* 15 was much greater than in any of the normal monkeys (chart 1), indicating that in these cases there was an abnormality in the curve for sugar as early as the first day after infection. On the second day the return to fasting levels was delayed, while during the third day the curves were flat and presented the same appearance as the venous curves of *M rhesus* 12 and M40 in chart 1.

To avoid the variations produced by the retention of dextrose in the stomach, the solution of dextrose was injected directly into the lumen of the small intestine of two normal monkeys. About 10 cm below the pylorus, the duodenum was exposed under aseptic conditions with a minimum of handling, the solution of dextrose was introduced through a fine needle, after the duodenum had been replaced, the abdominal wall was sewn up. Results from these two trials indicated that retention in the stomach was but one factor producing the flat or irregular curves shown in charts 1 and 2. In one case the maximum rise was 50 mg per hundred cubic centimeters, and in the other 12 mg. The blood sugar did not fall below fasting levels in one and one-half hours, and the general appearance of both curves resembled that of *M rhesus* M40.

Intravenous Injections of 1 Gm of Dextrose per Kilogram of Body Weight—In each case the solution of dextrose (from 4 to 7 cc of a 50 per cent solution) was injected into a vein of an arm or the saphenous vein in one minute. Chart 3 represents some of the tests in which venous blood alone was analyzed. It is evident from these curves and those in chart 4, that the reaction of normal monkeys after the intravenous administration of dextrose is far more regular and predictable than that after peroral administration, permitting more accurate evaluation of the disturbances caused by abnormal conditions.

A comparison of the curves for the normal and the sick monkeys reveals a much slower removal of dextrose from the blood of the sick monkeys. After ninety minutes the blood sugar of the normal animals had returned to fasting levels, while it was still high in the animals with yellow fever.

The urine of monkeys 1 and 5 was analyzed for sugar. Forty-five minutes after completion of the test, 10 cc of urine from normal monkey 1 (chart 3) contained 120 mg of sugar. In monkey 5, which

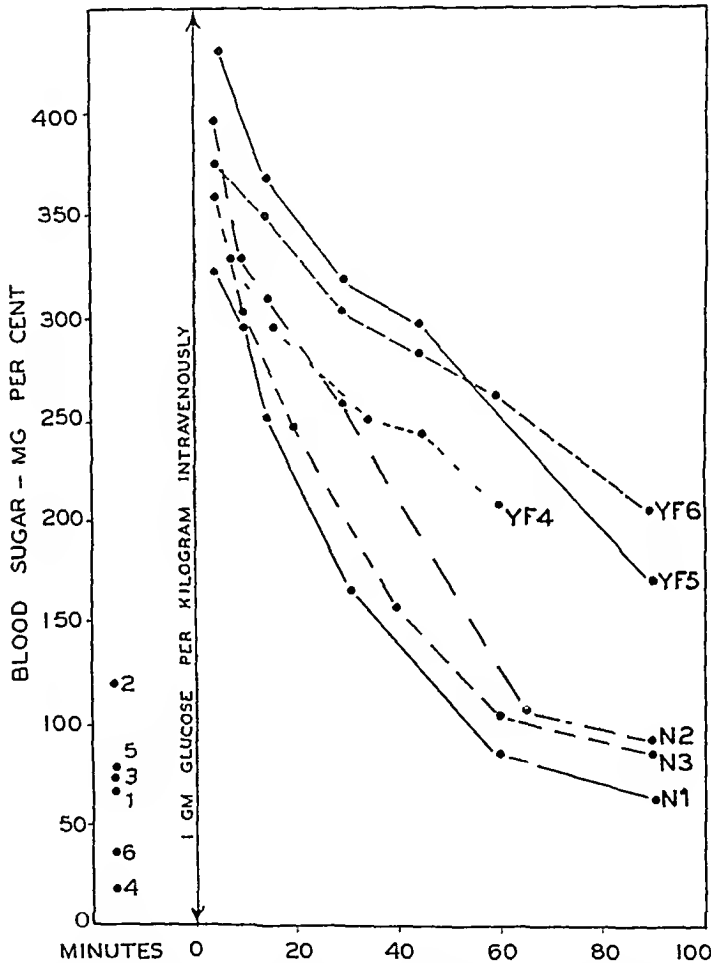


Chart 3—Curves showing the venous blood sugar of normal monkeys (*N*) and monkeys with yellow fever (*YF*), after the intravenous administration of 1 Gm of dextrose per kilogram

had yellow fever, at autopsy and fourteen hours after the last sample of blood was taken, 5 cc of urine from the bladder contained 130 mg of sugar. Hence the more rapid fall in blood sugar of the normal animal was not due to greater excretion in the urine.

Some figures obtained from arterial and venous blood of normal and sick monkeys, after the intravenous administration of dextrose, are given in chart 4. Both of the monkeys with yellow fever were prostrate

when the experiment began and died the same night. In monkey 9 at autopsy performed six hours after the completion of the test, 4 cc of urine contained 150 mg of sugar.

The results of these tests present two notable features: (1) the decline of blood sugar is slower in the sick monkeys, and (2) in the normal animals the arterial and venous curves cross each other, and they do not cross in the animals with yellow fever.

A part of the large arterial-venous differences encountered directly after injection may be due to the incomplete mixing of the blood. An increase in the venous blood sugar of *Monkeys* 10 between the six and

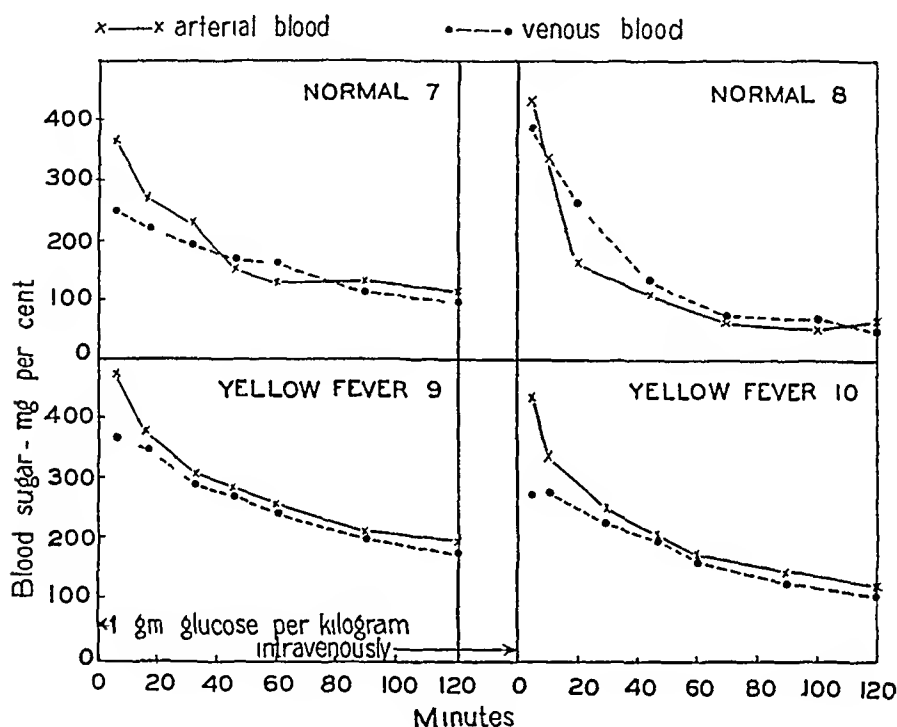


Chart 4—Curves showing the arterial and venous blood sugar of normal monkeys and monkeys with yellow fever, after the intravenous administration of 1 Gm of dextrose per kilogram.

sixteen minute interval lends support to this view. Nevertheless, since the tissues are rapidly taking up sugar at this time, as evidenced by the rapid fall in the concentration of blood sugar, large arteriovenous differences are to be expected.

Analysis of Blood From Various Parts of the Circulation—In the early experiments, before the technic of obtaining samples of arterial and venous blood simultaneously was perfected, the arterial blood was taken from one part of the body and the venous blood from another. Later a check on the concentrations of blood sugar in the various parts of the circulation was made. The results of this investigation have been collected in the accompanying table.

The animal used was a large male *Macacus rhesus* weighing 3.91 Kg. It was given the regular diet at 8 a. m., and when removed from the cage at 9 a. m., he had eaten a part of it. Sixty milligrams of amytal per kilogram of body weight was given intraperitoneally, and the right carotid artery and jugular vein were exposed. The femoral vein and artery on both legs were also dissected out. Blood samples from the different vessels were analyzed for sugar before and after 1 Gm of dextrose per kilogram of body weight was injected into the right femoral vein. Before injection, blood samples taken not more than a minute apart from the same vessel or different vessels, e. g., femoral vein and jugular vein, femoral artery and carotid artery, yielded almost identical results. The increase in the concentration of sugar in the venous blood between 10.12 a. m. and 10.35 a. m., may be ascribed to absorption from the intestinal tract. Following the injection of sugar there were some large divergences in samples of both venous and arterial blood drawn from different vessels. For example, at 10.45 a. m., blood from the left femoral vein contained 354 mg., while that from the right jugular vein contained 429 mg. per hundred cubic centimeters, a difference of 75 mg. per hundred cubic centimeters. This occurred six minutes after the sugar was injected. The difference is too large for experimental error and is probably due to incomplete mixing of the blood. That such differences do occur emphasizes the necessity of obtaining arterial and venous blood from comparable vessels, such as the femoral vessels of one leg. This precaution was observed in the experiments presented in this article.

If the average concentrations of arterial and venous blood sugar are plotted, the typical crossing and recrossing of the two curves, which were observed after the intravenous injection of dextrose into normal monkeys, becomes apparent.

COMMENT

The majority of the tests for sugar tolerance, following the oral administration of dextrose to a normal subject, which have been reported in the literature, have two features in common, namely, a rise of the blood sugar to a maximum level in from thirty to forty-five minutes, and a return to normal or subnormal levels in from one to three hours.⁷ We had hoped to observe the same phenomena in monkeys and had planned to use these figures as a basis of comparison for the reaction of similar animals ill with yellow fever. The considerable variation in the response of the different normal monkeys to dextrose administered orally made this plan unsatisfactory.

⁷ Hammon and Hirschman (footnote 3) Friedenson, Rosenbaum, Thalheimer and Peters (footnote 4) John (footnote 5) Gray, H. Blood Sugar Standards. Normal and Diabetic Persons, Arch Int Med **31** 241 (Feb) 1923.

Chart 1 shows the rather wide variation in the type of curve obtained, which renders it impossible to interpret with exactness the small changes one would expect to find early in the course of the disease. However, such objections are not so important when dealing with the response of very sick or moribund monkeys since they show little or no rise in blood sugar after the oral administration of dextrose. The results obtained from the injection of a solution of dextrose into the intestine, and particularly from the experiment with *M. rhesus* 16, indicate that slow absorption is an important factor in producing the flat curves exhibited by *M. rhesus* 12 and M40 in chart 1. If at least

Results of Test to Determine the Concentration of Blood-Sugar in Various Parts of the Circulation of a Macacus Rhesus

Time	Vessel	Blood Sugar Mg. per 100 Cc
10 11 a m	Right femoral vein	72
10 12 a m	Right femoral vein	71
10 17 a m	Right femoral artery	69
10 18 a m	Right femoral artery	69
10 23 a m	Right femoral artery	87
10 23 a m	Right carotid artery	67
10 35 a m	Right femoral vein	85
10 35 a m	Right jugular vein	87
*10 40-10 41 a m	Dextrose injected	
10 43 a m	Right femoral artery	345
10 45 a m	Left femoral vein	374
10 45 a m	Right jugular vein	429
10 54 a m	Left femoral artery	329
10 54 a m	Right carotid artery	340
11 01 a m	Right femoral artery	280
11 04 a m	Left femoral vein	281
11 04 a m	Right jugular vein	270
11 20 a m	Left femoral vein	218
11 20 a m	Right femoral vein	216
11 24 a m	Left femoral artery	202
11 24 a m	Right femoral artery	178
11 34 a m	Right femoral artery	131
11 34 a m	Left femoral vein	165
11 45 a m	Right femoral artery	108
11 45 a m	Left femoral vein	144
11 50 a m	Right carotid artery	100
	Duplicate on same sample	101
12 15 p m	Right femoral artery	101
12 15 p m	Left femoral vein	98

* Dextrose injected into right femoral vein

one half of a small dose of dextrose remains for six and one-half hours in the intestinal tract of a monkey in the early stage of yellow fever, it is probable that a still larger proportion could be found unabsorbed in a prostrate animal.

An indication of progressive failure in ability to handle ingested carbohydrate is shown in the results from *M. rhesus* 14 and 15 (chart 2). Since both monkeys had a short course of fever and survived only four and three days, respectively, after inoculation the degeneration of the liver must have been rapid. Even on the first day after infection the curves for blood sugar vary in one respect from the normal, the maximum rise, 165 and 115 mg per hundred cubic centimeters, respectively, in venous blood, is greater than that usually

observed for a normal monkey, from 25 to 85 mg per hundred cubic centimeters after the same dose. On the following day, which was the first day of fever, further alterations were apparent. The blood sugar of *M rhesus* 14 rose about 165 mg per hundred cubic centimeters in the first twenty minutes after injection and then fell rather slowly to 210 mg per hundred cubic centimeters in ninety minutes. This slow fall of blood sugar following injection in yellow fever is well illustrated in chart 3. The blood sugar of *M rhesus* 15 rose to 350 mg, an increase of 210 mg per hundred cubic centimeters above the fasting level, in forty minutes after ingestion, and was still 200 mg per hundred cubic centimeters at the end of ninety minutes. Both the peak of this curve for blood sugar and the value at the end of one and one-half hours are considerably higher than corresponding values obtained with normal monkeys. While the blood sugar of these two animals during fasting was still within the normal range,⁸ a distinct abnormality in the curves for blood sugar after the ingestion of dextrose is evident. On the last day of the experiment, when both animals were obviously ill, curves were obtained that are quite like the others from moribund monkeys shown in chart 1. The curves on both animals are flat, and no maximum is obtained in the first hour after the ingestion of sugar. At this time the blood sugar of both animals during fasting was low, particularly in the case of *M rhesus* 15, which died several hours before *M rhesus* 14. In general, the two monkeys showed a tolerance for sugar that decreased with the progress of the disease, while the results of the bromsulphonphalein tests reveal a corresponding decline in the function of the liver, probably due to the hepatic lesions of yellow fever.

The slow fall of blood sugar noted in the experiment with *M rhesus* 14 on December 12 (chart 2), is confirmed by the results of intravenous injection (chart 3). In the normal animals, blood sugar reached fasting levels in ninety minutes, while in the sick monkeys it remained elevated longer. The slower fall of venous blood sugar in yellow fever is not due to lack of diffusion into the tissues, since arterial-venous differences in these animals are as great as in the normal animals and persist for an even longer time (chart 4), and it is not due to a smaller excretion in the urine, since *M rhesus* 5 excreted a trifle more than *M rhesus* 1. Indeed it seems doubtful that excretion was a significant factor in either case. The urine of two sick monkeys not previously mentioned contained only 340 and 305 mg following injections of 1 Gm of dextrose per kilogram, and another normal monkey excreted no sugar after the same dose. In this connection, Kleiner⁸ found that sugar disappeared from the blood of nephrectomized and normal dogs

⁸ Kleiner, I. S. The Disappearance of Dextrose from the Blood After Intravenous Injection, *J. Exper. Med.* **23**: 507, 1916.

at the same rate following intravenous injections. The rapid fall of blood sugar immediately after intravenous injections is best accounted for by distribution to the tissues, and the large arterial-venous differences support the view.

Briefly, the sequence of events following the intravenous injection of dextrose is (1) a rapid fall of the blood sugar brought about by diffusion of dextrose into muscle, skin, liver and other tissues, (2) a redistribution of the sugar from muscle, skin and subcutaneous tissues to other organs, notably the liver, there to be used in the formation of glycogen, (3) further formation of glycogen by the muscles, with a coincident withdrawal of sugar from the blood.

The alterations of arterial and venous blood sugar are consistent with this explanation. The remarkable feature of the sugar curves presented in chart 4 is the crossing of the arterial and venous curves in the normal animal and the fact that they do not cross in the animals with yellow fever. The significance of this difference is that in yellow fever the liver is capable of forming little or no glycogen, and hence the sugar is not withdrawn from the blood so rapidly as in the normal animals. This assumption is validated by finding only traces of glycogen in the livers of monkeys dying with yellow fever.⁶ In normal monkey 7 (chart 4), the immediate distribution of dextrose to the tissues is evidenced by the large positive differences between the values for arterial and venous blood sugar obtained in the first forty minutes after injection. A similar reaction occurred in monkey 9, ill with yellow fever. However, after forty minutes the arteriovenous differences in monkey 7 became negative, while in monkey 9 they remained positive throughout the experiment. During the second forty minutes of the experiment with monkey 7, sugar was being removed from the muscles by the blood and presumably carried to the liver for the formation of glycogen. Since glycogenesis in the liver of monkey 9 was proceeding slowly or not at all, the reversal of arteriovenous differences in blood sugar was not evident. Still later in the experiment, when the blood sugar was approaching fasting levels, glycogenesis made itself evident in the muscles, and there was a second reversal of the arteriovenous differences.

Thus the outstanding distinctions between the reactions to the tests for sugar tolerance of normal monkeys and those ill with yellow fever are the slower fall of the blood sugar level and the lack of reversal of the arteriovenous differences in blood sugar in the sick animals. Both of these variations can be accounted for by the inability of the liver to form glycogen.

SUMMARY

1. The response of the blood sugar of normal monkeys to dextrose administered perorally is irregular. Monkeys very ill with yellow fever show practically no increase in blood sugar after the ingestion of 1 Gm

of dextrose per kilogram, chiefly because in this condition sugar is absorbed extremely slowly, if at all, from the alimentary canal

2 Tolerance for sugar is diminished in yellow fever before the monkeys become prostrate

3 Dextrose injected intravenously is not so rapidly removed from the blood of monkeys ill with yellow fever as from the blood of normal monkeys

4 In normal monkeys, after the intravenous injection of dextrose, accelerated glycogenesis in the liver is manifested by a crossing of the curves for arterial and venous blood sugar as the initial hyperglycemia subsides. Crossing of the curves is absent in yellow fever, indicating loss of hepatic function

THE RÔLE OF ARTICHOKES IN THE DIET OF THE DIABETIC PATIENT ~

HERMANN [†]B STEIN, M D

BERNARD B LONGWELL, A B [†]

AND

ROBERT C LEWIS, P H D

DENVER

At various times Jerusalem artichokes have been advocated in the diet of the diabetic patient. The tuber is rich in inulin, which on hydrolysis yields levulose, a monosaccharid to which is attributed the peculiar power of easier assimilation than dextrose. Joslin¹ expressed the belief that this may be due to the conversion of a portion of the levulose to fat or to a more active stimulation of the production of insulin.

A word may not be amiss here concerning the name and history of the plant. The following information is contained in an article by Shoemaker². The Jerusalem artichoke, *Helianthus tuberosus* L., is widely known but little used in the United States. Champlain found the tuber growing in the gardens of the Indians at Mallebarre (now Nauset Harbor, Cape Cod, Mass.) on July 21, 1604. Lescaibot, a companion of Champlain, probably introduced it into France. Plants similar in growth and flowering to many of the present day varieties grown at Washington, D. C., were described and pictured by Colonna in 1616 as occurring in the garden of Cardinal Farnese at Rome. The name, "Jerusalem artichoke," has been a source of continual comment, since it is neither descriptive nor true. For many years the first word has been explained as an English corruption of the Italian word "girasole" meaning, at present, sunflower. The resemblance in flavor of the Jerusalem artichoke to the true artichoke has accounted for the latter half of the name.

The plant is widely distributed throughout the United States. Its range of growth is usually given as from New York to Minnesota and southward to Georgia and Arkansas. More recently its cultivation has been introduced into Colorado, Oregon and California.

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[†] From the Department of Biochemistry, University of Colorado School of Medicine

[†] Research fellow under a grant from Pabst Dietary Products, Inc

1 Joslin, E. P. The Treatment of Diabetes Mellitus, ed 4, Philadelphia, Lea & Febiger, pp 630-631

2 Shoemaker, D. N. The Jerusalem Artichoke as a Crop Plant. Tech Bull no 33, U. S. Dept of Agriculture, Washington, D. C., October, 1927

In spite of repeated investigations, divergencies still exist as to the nature and relative proportions of the carbohydrates found in the tuber. This is probably due to the fact that the various analyses have been made on tubers that have been collected at different seasons of the year and stored for varying lengths of time. Any one who is at all familiar with this vegetable knows that immediately after frost there is a marked increase in its sugar content. Prior to that time, the raw tuber has an insipid taste, as soon as frost occurs, it becomes sweet and acquires an improved flavor. The most complete report on the nature of the carbohydrates is the recent contribution of Thaysen, Bakes and Green³ who concluded that the unripe, autumn-gathered tuber contains a large amount of an insoluble, nonfermentable carbohydrate apparently identical with inulin, which disappears almost completely toward spring, giving way to increased proportions of the more soluble

TABLE 1—*Percentage of Distribution of Carbohydrates in the Jerusalem Artichoke (Helianthus tuberosus L.) Calculated on the Basis of the Total Carbohydrates Present**

Tubers Harvested		Inulin and Pseudo Inulin, per Cent	Simpler Carbohydrates, per Cent
Sept	Oct, 1892†	84.66†	15.34
November,	1923	41.44	58.56
March,	1924	1.02	98.98

* From Thaysen, Bakes and Green (footnote 3)

† Analysis taken from Tanret (footnote 4)

‡ Includes inulin, helianthin and synanthrin, carbohydrates similar to inulin, but not separated by the analyses of Thaysen, Bakes and Green

carbohydrates that are already present to a slight extent in the autumn tuber. Table 1 gives analyses taken from this paper to show how changes occur in the carbohydrates with the ripening of the tuber.

The question of the fermentability of inulin and related carbohydrates should receive some consideration, as fermentation may play an important part in the assimilability of the more complex carbohydrates of the artichoke. Although inulin itself is unfermentable by yeast, Tanret⁴ reported that it was fermented when present in a solution of already fermenting carbohydrates, an observation that was confirmed by Thaysen, Bakes and Green³. Moreover, the latter investigators found that a comparatively mild autoclaving without the use of acid hydrolysis is sufficient to render inulin fermentable by yeast.

Thus, the literature shows that tubers of Jerusalem artichokes that have been allowed to remain in the ground until the plant has been

3 Thaysen, A. C., Bakes, W. E., and Green, B. M. On the Nature of the Carbohydrates Found in the Jerusalem Artichoke, *Biochem J.* **23** 444, 1929.

4 Tanret. *Bull. Soc. chim. de France* **9** 622, 1893 (cited by Thaysen, Bakes and Green, footnote 3).

killed by frost contain a relatively high percentage of digestible carbohydrates, that autoclaving will hydrolyze some of the higher carbohydrates and that fermentation of inulin by yeast may occur in the presence of fermenting carbohydrates. From the latter facts, it seems probable that ordinary cooking may render digestible some of the more complex carbohydrates that are left in partially ripened tubers, and that inulin may behave in the presence of bacterial fermentation of other carbohydrates as it does with the fermentation by yeast under such conditions.

In 1923, Joslin and Root⁵ reported that the feeding of 15 Gm of inulin in the form of Jerusalem artichokes did not produce glycosuria in the diabetic person. Root and Baker⁶ obtained beneficial results in a group of patients over a period of six months and concluded that, in the amounts given, the Jerusalem artichoke could be added to the diets without increasing the glycosuria, when it was present, or producing it when previously absent. In certain cases, when the tubers were substituted for the other carbohydrates in the diet, glycosuria disappeared. Carpenter and Root⁷ studied intensively the effect of the Jerusalem artichoke on a person with diabetes mellitus when the tuber furnished half of the carbohydrate in the diet. This case is also mentioned elsewhere by Joslin,¹ and both writers were enthusiastic about the utilization of the carbohydrates of the artichoke by the diabetic patient. However, Westcott and Wise,⁸ using one subject over a period of eighteen days, reported negative results and concluded that dried artichokes have no advantage as a diabetic food.

Our interest in the subject was aroused by the reports of several physicians that they had found the Jerusalem artichoke to be of tremendous value in the dietetic control of diabetes. The controversial nature of the reports in the literature previously cited convinced us of the importance of further investigation.

EXPERIMENTAL DATA

Beginning in January, 1930, the effect of feeding artichokes to a group of diabetic patients in the Colorado General Hospital⁹ of the University of Colorado School of Medicine was studied. The procedure adopted was to place a patient

5 Joslin, E. P., and Root, H. F. Levulose and the Diabetic Metabolism, *J. A. M. A.* **80** 1727 (June 9) 1923.

6 Root, H. F., and Baker, M. L. Inulin and Artichokes in the Treatment of Diabetes, *Arch. Int. Med.* **36** 126 (July) 1925.

7 Carpenter, T. M., and Root, H. F. The Utilization of Jerusalem Artichokes by a Patient with Diabetes, *Arch. Int. Med.* **42** 64 (July) 1928.

8 Westcott, L. E., and Wise, E. C. Failure of a Diabetic Patient to Utilize Dried Artichoke Powder, *Arch. Int. Med.* **44** 362 (Sept.) 1929.

9 During the period of hospitalization all patients were on the medical service of Dr. Charles N. Meader.

on an adequate diabetic diet and to adjust the intake of carbohydrate so that a definite but slight glycosuria of moderate variation would result. Although the accomplishment of this might require a number of days, or even as long as three or four weeks, every care was made to establish the patient's tolerance before proceeding with the feeding of the artichokes. Not until a glycosuria with a variation of only a few grams in the daily average output of sugar was obtained, could it be considered safe to study the effect of artichokes in the diet. Then they were introduced either by substituting the carbohydrates of the artichoke for other carbohydrates or by superimposing them on the carbohydrate already present. None of the patients received insulin at any time during the experimental period. Thus, by the method adopted, it was possible to determine, from a study of any change that might occur in the amount of sugar excreted when the artichokes were fed, whether or not they had had any influence on the subject's tolerance for carbohydrates.

The artichoke products¹⁰ used had been prepared and preserved for commercial distribution by different processes. All were made from tubers that had remained in the ground until the plants had been killed by frost. Several kinds of preparations were fed in order to furnish variety to the patient. Puree, which consisted of the ground artichoke preserved in its own juice after sterilization

TABLE 2—*Analyses of Jerusalem Artichoke Products*^{*}

	Dried Slices, per Cent	Puree, per Cent	Flakes, per Cent
Moisture	3.81	77.20	2.03
Fat	0.43	0.60	30.02
Carbohydrate	67.27	17.20	52.20
Protein	7.59	2.20	4.41
Mineral salts	7.03	1.50	3.15
Cellulose and undetermined	13.87	1.30	7.24

^{*} Furnished by Pabst Dietary Products, Inc.

with steam, dehydrated slices, dried in vacuo at moderately low temperatures, and artichoke flakes, similar to potato flakes and made by cooking the freshly sliced tubers in cottonseed oil, were used. Table 2 gives analyses of the Jerusalem artichoke products as furnished by the manufacturer.

The flakes were fed as received. The puree was served as a soup, or as a vegetable after seasoning with salt, pepper and butter, and cooking down to a more solid consistency. The dried slices were made palatable by steaming, or by cooking in a casserole, with such foods as cheese, shrimp, meat or various vegetables, and by appropriate seasoning. The flakes were found to be the most palatable and the patients were able to consume more artichokes in this form without discomfort than when the other products were eaten.

During the first few days of the feeding of artichokes, the patients experienced considerable abdominal distress from the formation of gas. If the amount of artichokes in the diet was not increased too rapidly, these symptoms were ameliorated to a great extent and, subsequently, it was usually possible to give large quantities of artichoke products, particularly if the greater amount was in the form of flakes, without a recurrence of marked discomfort.

A careful record was made of the intake of food of each patient, and specimens of urine were collected at intervals of twenty-four hours throughout the experimental period. Quantitative determinations of the sugar excreted were made

¹⁰ All of the artichoke products were supplied by Pabst Dietary Products, Inc.

by the Benedict method¹¹ The urine was tested daily for acetone by the Legal method and for diacetic acid by the Gerhardt method Total nitrogen was determined by the Kjeldhal method, both as a check on whether or not we had received a complete twenty-four hour specimen and so that we might later refer to the metabolism of nitrogen, if the artichokes were found to have any influence on the diabetic condition of the patient At frequent intervals, blood was drawn before breakfast, and sugar was determined by the procedure of Folin-Wu¹² as modified for use with the Peebles-Lewis colorimeter¹³

The patients studied were recruited from the outpatient department of the hospital, and only those from whom satisfactory cooperation could be expected were used The cases varied from the mild to the moderate type of diabetes The following representative cases are reported

REPORT OF CASES

CASE 1—G W, a boy, aged 15, weighing 147 pounds (66.7 Kg), had had influenza at 13, followed by "kidney trouble," defective vision and puffiness below the eyes In March, 1929, he fell from a ladder on a school playground, at which time he wrenched his right side and bruised the right side of his face, but suffered no loss of consciousness Soon after the fall he noticed the first symptoms of diabetes, namely, polyuria, polydipsia and marked loss of weight No treatment was instituted until September, when he was hospitalized Under a regulated diet and the administration of insulin, he responded satisfactorily and was discharged after one month At home he became careless in controlling his diet When he first came under the care of Dr Stein early in November, he was living on a normal diet, taking 20 units of insulin every day The blood sugar was 272 mg per hundred cubic centimeters, and the twenty-four hour specimen of urine showed 227 Gm of dextrose On a diet of 50 Gm of carbohydrate, 75 of protein and 150 of fat the glycosuria was controlled in six days, and the necessity of using insulin was eliminated in ten more days When the patient entered the Colorado General Hospital on Jan 7, 1930, for observation during the feeding of artichokes, the urine was sugar-free The diet was increased gradually to produce glycosuria On February 16, he was getting 400 Gm of carbohydrate, 80 of protein and 120 of fat, and was excreting such a fairly constant amount of dextrose daily that he was considered ready for study Table 3 gives data concerning the diet and laboratory observations in this case during the experimental period Subsequent to the discharge from the hospital, this patient was observed in the outpatient department of the School of Medicine and continued in first class condition without the administration of insulin for the several weeks that followed

CASE 2—In A R, a woman, aged 25, weighing 106 pounds (48.1 Kg), sugar was found in the urine during an influenza attack a year previously, but no treatment was instituted by the attending physician During the preceding few months

11 Benedict, S R A Method for the Estimation of Reducing Sugars, *J Biol Chem* 9 57, 1911

12 Folin, O, and Wu, H A System of Blood Analysis Supplement I A Simplified and Improved Method for Determination of Sugar, *J Biol Chem* 41 367, 1920

13 Peebles, A R, and Lewis, R C A Simple and Accurate Colorimeter for Clinical Use, *J A M A* 70 679 (March 9) 1918 Lewis, R C Two Improved Designs of the Peebles-Lewis Clinical Colorimeter, *J Lab & Clin Med* 16 914 (June) 1931

TABLE 3—Data Concerning the Diet and Laboratory Observations in G W

Date, 1930	Weight, Pounds	Urine			Blood Sugar, Mg	Diet					Calories
		Vol ume, Ce	Nitro gen, Gm	Sugar, Gm		Pro tein, Gm	Fat, Gm	Carbohydrate			
								Total, Gm	Artiehoke, Gm		
2/15	142	2,070	7.9	3.7		80	120	400		3,000	
2/16	142	2,545	9.2	4.8		80	120	400		3,000	
2/17	142	2,330	7.9	3.1		80	120	400		3,000	
2/18	142	2,360	10.6	2.9		80	120	400		3,000	
2/19	142	1,420	6.7	1.7	88	80	120	400	20 Subst	3,000	
2/20	142	2,140	9.1	3.8		80	120	400	20 Subst	3,000	
2/21	143	2,075	6.5	6.9		80	120	400	20 Subst	3,000	
2/22	143	1,505	8.3	2.8		80	120	400	20 Subst	3,000	
2/23	143	3,180	11.2	3.1		80	120	400	40 Subst	3,000	
2/24	143	1,565	5.5	3.5		80	120	400	40 Subst	3,000	
2/25	143	2,680	7.5	3.3	98	80	120	400	40 Subst	3,000	
2/26	144	2,010	8.3	4.1		80	120	100	40 Subst	3,000	
2/27	144	2,210	9.3	3.1		80	120	400	70 Subst	3,000	
2/28	144	2,475	8.5	8.4		80	120	400	70 Subst	3,000	
3/ 1	145	2,325	9.3	2.5		80	120	400	70 Subst	3,000	
3/ 2	145	2,015	8.1	2.7		80	120	400	100 Subst	3,000	
3/ 3	145	2,280	8.5	4.3	107	80	120	400	100 Subst	3,000	
3/ 4	144	1,755	5.6			80	120	400	100 Subst	3,000	
3/ 5	144	2,390	8.1			80	120	400		3,000	
3/ 6	144	2,430	8.1	6.6		80	120	100		3,000	
3/ 7	144	2,355	8.7	10.0		80	120	400		3,000	
3/ 8	144	2,195	7.1	6.0		80	120	120	20 Added	3,080	
3/ 9	146	3,355	9.2	32.1		80	120	420	20 Added	3,080	
3/10	146	2,795	8.6	10.0		80	120	420	20 Added	3,080	
3/11	146	2,735	10.1	41.1	140	80	120	420	20 Added	3,080	
3/12	144	2,940	10.2	67.0		80	120	420	20 Added	3,080	
3/13	145	3,000	8.4	44.3	170	80	120	420	20 Added	3,080	
3/14	145	3,075	9.0	91.5		80	120	420	20 Added	3,080	
3/15	145	1,420	8.7	26.0	168	80	120	400		3,000	
3/16	145	2,520	10.2	40.4		80	120	400		3,000	
3/17	145	2,555	7.0	77.0	178	80	120	400		3,000	
3/18	145	2,445		56.6		80	120	400	100 Subst	3,000	
3/19	145	4,526	16.7	132.1	212	80	120	400	100 Subst	3,000	
3/20	145	2,010	6.5	60.6		80	120	400	100 Subst	3,000	
3/21	145	2,060	9.0	60.3	218	80	120	400	100 Subst	3,000	
3/22	145	1,655	7.9	46.3		80	120	400	100 Subst	3,000	
3/23	145	2,085	8.9	64.6		80	120	400	100 Subst	3,000	
3/24	146	1,660	9.0	74.8	208	80	120	400	100 Subst	3,000	
3/25	145	2,240	8.9	87.2		80	120	400	100 Subst	3,000	
3/26	145				228	80	120	400	200 Subst	3,000	
3/27	145	1,640	7.4	30.4		80	120	400	200 Subst	3,000	
3/28	145	1,540	7.0	17.6	210	80	120	400	200 Subst	3,000	
3/29	145	1,710	7.2	33.8		80	120	400	200 Subst	3,000	
3/30	145	1,310	6.8	41.2		80	120	400	200 Subst	3,000	
3/31	145	2,520	5.4	37.1	190	80	120	400	200 Subst	3,000	
4/ 1	145	1,425	5.6	20.1		80	120	400	200 Subst	3,000	
4/ 2	145	2,420	8.8	81.9	220	80	120	400	200 Subst	3,000	
4/ 3	145	1,610	6.5	61.1		80	120	400	200 Subst	3,000	
4/ 4	145	2,120	6.2	119.6	236	80	120	370		2,800	
4/ 5	145	1,790	8.6	115.8		80	120	350		2,800	
4/ 6	145	2,230	10.8	99.0		80	120	300		2,600	
4/ 7	145	2,040	7.1	113.9		80	120	300		2,600	
*4/ 8	144	2,365	6.5	129.0	214	80	120	300		2,600	
4/ 9	143	2,395	9.7	145.3		80	120	300		2,600	
4/10	144	2,020	12.2	145.9	252	80	120	250		2,400	
4/11	144	1,800	12.9	137.3		80	120	250		2,400	
4/12	143	1,635	16.0	81.4	180	80	120	150		2,000	
*4/13	141	1,855	15.0	23.8		80	120	75		1,700	
4/14	140	1,835	10.9	24.4	210	80	120	75		1,700	
4/15	138	1,560	11.6	8.4		80	120	75		1,700	
4/16	138	1,995	10.4	10.2		80	120	75		1,700	
*4/17	137	2,610	7.4	14.9		80	120	75		1,700	
4/18	137	2,285	13.6	8.2		80	150	75		1,970	
*4/19	137	2,900	18.9	23.5	184	80	150	75		1,970	
4/20	137	2,840	16.1	14.4		80	150	75		1,970	
4/21	137	2,040	13.9	12.2		80	150	75		1,970	
4/22	136	1,950	13.5	Trace		75	150	50		1,850	
4/23	135	2,350	13.5			75	150	50		1,850	
4/24	135	2,445	12.2			75	150	50		1,850	
4/25	135	1,800	12.3		190	75	150	50		1,850	
4/29					116						

* Acetone present in urine (tests were made daily)

TABLE 4—Data Concerning the Diet and Laboratory Observations in A R

Date, 1930	Weight, Pounds	Urine				Blood Sugar, Mg	Diet					Calories
		Vol ume, Cc	Nitro gen, Gm	Sugar, Gm	Pro tein, Gm		Fat, Gm	Carbohydrate				
								Total, Gm	Artiehoke, Gm			
2/22	110	1,240		7 6		50	150	50			1,750	
2/23	109	930	3 3	2 4		50	150	50			1,750	
*†2/24	106	1,555	7 1	2 6	116	50	150	50			1,750	
*†2/25	106	1,720	6 8	1 8		50	150	50			1,750	
*†2/26	105	1,530	5 8	1 7		50	150	60			1,790	
*†2/27	107	1,540	6 0	2 3		50	150	60			1,790	
*†2/28	107	2,185	5 9			50	150	60	20 Subst		1,790	
*†3/ 1	107	2,475	7 2	1 9		50	150	60	20 Subst		1,790	
*†3/ 2	107	2,490	5 5	1 8		50	150	60	30 Subst		1,790	
†3/ 3	106	3,115	4 5		113	50	150	60			1,790	
3/ 4	106	2,015	5 4	16 7		55	150	175			2,270	
3/ 5	107	2,355	3 1	3 1		50	150	60			1,790	
3/ 6	108	3,055	4 7	2 3		50	150	80	20 Added		1,870	
3/ 7	108	2,205	4 6			50	150	80	20 Added		1,870	
3/ 8	108	2,110	4 7			50	150	80	20 Added		1,870	
†3/ 9	108	2,815	4 8			50	150	80	20 Added		1,870	
†3/10	109	1,905	4 5			50	150	100	40 Added		1,950	
†3/11	109	2,505	3 8		126	50	150	100	40 Added		1,950	
†3/12	108	1,955	4 0			50	150	140	80 Added		2,110	
3/13	110	2,835	5 1		107	50	150	140	80 Added		2,110	
†3/14	111	2,135	3 5			50	150	140	80 Added		2,110	
3/15	110	2,085	4 5		109	50	150	160	100 Added		2,190	
3/16	111	1,975	4 3			50	150	160			2,190	
3/17	111	2,935	3 8	2 0	124	50	150	180			2,270	
3/18	111	3,450		1 9		50	150	190			2,310	
3/19	110	2,620	4 5		130	50	150	200			2,350	
3/20	111	2,725	4 4			50	150	200			2,350	
3/21	110	3,300	4 6		148	50	150	200			2,350	
3/22	110	3,210	5 5	5 6		50	150	210			2,390	
3/23	110	3,200	6 2	8 2		50	150	220			2,430	
3/24	110	3,040	5 6	Trace	156	50	150	220			2,430	
3/25	110	2,095	5 8			50	150	220			2,430	
3/26	111	2,025	3 5		138	50	150	220	100 Subst		2,430	
3/27	112	2,250	3 9			50	150	220	100 Subst		2,430	
3/28	111	1,540	3 3		124	50	150	220	100 Subst		2,430	
3/29	112	3,180	4 0			50	150	220			2,430	
3/30	110	1,880	3 7			50	150	220			2,430	
3/31	110	2,025	4 3	Trace	127	50	150	320	100 Added		2,830	
4/ 1	111	2,760	3 9			50	150	320	100 Added		2,830	
4/ 2	111	2,025	4 4	3 6	142	50	150	320	100 Added		2,830	
*4/ 3	111	970	3 6	10 2		50	150	320	100 Added		2,830	
4/ 4	111	2,400	4 8	17 0	144	54	181	252			2,853	
4/ 5	112	1,700	4 8	7 2		54	181	252			2,853	
4/ 6	111	2,180	4 3	3 6		54	181	200			2,645	
4/ 7	111	1,690	4 4	1 4		54	181	200			2,645	
4/ 8	110	3,125	5 8	Trace	172	54	181	200			2,645	
4/ 9	110	2,655	6 8	24 1		54	181	200			2,645	
4/10	111	2,635	5 4	3 1	188	50	125	150			1,925	
*4/11	111	2,585	5 0	13 9		54	125	200			2,141	
4/12	110	2,025	4 5	6 3	224	54	125	200			2,141	
4/13	110	2,050	4 1	3 0		50	125	100			1,725	
4/14	110	2,515	4 6		156	50	125	100			1,725	
4/15	110	1,985	5 0			50	125	100			1,725	
4/16	110	1,645	4 5			52	140	126	26 Added		1,972	
4/17	110	1,735	5 0	2 2		52	140	126	26 Added		1,972	
4/18	110	2,035	4 4			52	140	126	26 Added		1,972	
4/19	110	2,300	6 2	Trace	138	52	140	126	26 Added		1,972	
4/20	110	1,855	5 2	Trace		52	140	126	26 Added		1,972	
4/21	109	2,370	4 9			52	140	126	26 Added		1,972	
4/22	110	2,125	6 1			52	140	126			1,972	
4/23	109	1,915	4 7			52	140	126			1,972	
4/24	110	1,625	4 5			52	140	126			1,972	

* Diaetic acid present in urine (tests were made daily)

† Acetone present in urine (tests were made daily)

she had lost 10 pounds (4.5 Kg). She was hungry and thirsty all of the time and had polyuria to such a degree that it was necessary for her to urinate four or five times each night. She complained that the skin of the face and lips seemed dry and the mouth parched. She was admitted to the hospital for study on Feb 22, 1930. Complete data concerning the diet and laboratory observations made during the period of hospitalization and experimental study are given in table 4.

CASE 3—C. J., a woman, aged 49, weighing 152 pounds (68.9 Kg), had had influenza during the winter of 1929 from which convalescence was slow. Soon afterward an abscess developed in the soft tissue at the base of the spine. The attending physician examined the urine and discovered that sugar was present. The patient was then placed on a diet restricted in carbohydrates, without insulin. In December, she came under our care and was hospitalized on Jan 8, 1930. Examination of the blood on that day showed 196 mg of sugar, on January 13, 242 mg, on January 22, 192 mg, on January 28, 164 mg, and on February 3, 164 mg per hundred cubic centimeters. During this time the diet was being regulated so that a fairly constant amount of urinary sugar would be excreted before the feeding with artichokes began. Data relative to the dietary regimen and laboratory observations are given in table 5.

COMMENT

In this group of patients, after a fairly constant level of sugar excretion was obtained the Jerusalem artichokes were included in the diet (1) by substitution for other carbohydrates to determine whether or not the carbohydrates of the artichoke would be better metabolized in the diabetic organism and (2) by addition to the diet as a further means of testing whether or not the artichoke contained some principle similar to the glucokinin of Collip,¹⁴ which would stimulate better combustion of the carbohydrate fed.

In G. W. (table 3), there was no appreciable change in the diabetic condition even when as much as 100 Gm of artichoke carbohydrate, equivalent to 25 per cent of the total carbohydrate was substituted. When as little as 20 Gm of the artichoke carbohydrate was given in addition to the other carbohydrate the patient excreted larger amounts of sugar than at any time previously and the blood sugar rose sharply. Vain efforts were made to bring this patient back to his former condition both by omitting the added carbohydrate and by substituting artichokes in the diet not until a marked decrease in the intake of carbohydrates was made, however did the urine become free from sugar, and the blood sugar return to normal. We cannot account for the marked decrease in tolerance, which resulted when 20 Gm of artichoke carbohydrate was added to the diet of this patient and which necessitated a marked reduction in the intake of carbohydrate before

¹⁴ Collip J. B. Glucokinin. A New Hormone Present in Plant Tissue. Preliminary Paper, J Biol Chem 56:513, 1923, Glucokinin J Biol Chem 57:65, 1923.

TABLE 5—Data Concerning the Diet and Laboratory Observations in C J

Date, 1930	Weight, Pounds	Urine			Blood Sugar, Mg	Diet				
		Vol ume, Ce	Nitro gen, Gm	Sugar, Gm		Pro tein, Gm	Fat, Gm	Total, Gm	Artichoke, Gm	Calories
2/ 8	152	2,740	6 9	8 9		50	140	200		2,260
2/ 9	152	3,375	8 3	7 8		50	140	200		2,260
2/10	152	3,135	7 4	5 9		50	140	200		2,260
2/11	152	2,535	6 9	11 2	168	50	140	200		2,260
2/12	152	2,550	6 0	7 8		50	140	200	20 Subst	2,260
2/13	152	2,975	7 0	7 9		50	140	200	20 Subst	2,260
2/14	153	2,290	7 2	10 8		50	140	200	20 Subst	2,260
2/15	153	2,605	6 3	4 9		50	140	200	20 Subst	2,260
2/16	152	3,145	6 4	10 6		50	140	200	20 Subst	2,260
2/17	152	2,185	5 5	8 0		50	140	200	20 Subst	2,260
2/18	153	3,115	8 1	6 9		50	140	200	20 Subst	2,260
2/19	152	2,505	6 1	7 3	160	50	140	200	40 Subst	2,260
2/20	153	2,355	5 7	8 6		50	140	200	40 Subst	2,260
2/21	154	2,430	5 1	5 6		50	140	200	40 Subst	2,260
2/22	152	2,400	5 6	3 9		50	140	200	40 Subst	2,260
2/23	154	2,250	6 5	12 2		50	140	200	70 Subst	2,260
2/24	153	1,755	6 0	8 5		50	140	200	70 Subst	2,260
2/25	155	2,385	6 4	6 6	134	50	140	200	70 Subst	2,260
2/26	154	2,490	6 8	10 1		50	140	200	70 Subst	2,260
2/27	155	2,200	5 6	4 5		50	140	200	100 Subst	2,260
2/28	155	1,965	6 2	4 2		50	140	200	100 Subst	2,260
3/ 1	155	1,475	4 8	4 6		50	140	200	100 Subst	2,260
3/ 2	156	1,815	5 5	2 4		50	140	200	100 Subst	2,260
3/ 3	155	2,500	4 5	3 8	154	50	140	200	100 Subst	2,260
3/ 4	155	2,515	5 8	13 3		50	140	200		2,260
3/ 5	155	1,575	5 3	17 3		50	140	200		2,260
3/ 6	153	3,065	6 8	20 4		50	140	200		2,260
3/ 7	154	1,965	6 6	26 2		50	140	200		2,260
3/ 8	154	2,405	6 8	31 0		50	140	220	20 Added	2,340
3/ 9	155	2,435	7 1	16 4		50	140	220	20 Added	2,340
3/10	154	2,135	7 7	11 2		50	140	220	20 Added	2,340
3/11	155	2,070	6 8	9 7	172	50	140	220	20 Added	2,340
3/12	154	2,565	6 7	10 4		50	140	220	20 Added	2,340
3/13	155	1,725	5 6	9 6	144	50	140	220	20 Added	2,340
3/14	155	2,240	7 0	20 1		50	140	220	20 Added	2,340
3/15	155	2,200	4 9	16 3	170	50	140	220	20 Added	2,340
3/16	155	2,010	5 8	13 3		50	140	220	20 Added	2,340
3/17	155	1,810	7 0	6 2	168	50	140	220	20 Added	2,340
3/18	155	1,980		13 4		50	140	220		2,340
3/19	155	2,820	7 3	14 1	196	50	140	220		2,340
3/20	156	2,630	6 2	16 7		50	140	220		2,340
3/21	156	1,960	6 8	17 7	174	50	140	220		2,340
3/22	156	1,865	6 6	19 3		50	140	220		2,340
3/23	156	2,490	6 8	26 4		50	140	220		2,340
3/24	154	1,900	8 5	31 0	188	50	140	220		2,340
3/25	156	1,560	7 9	25 0		50	140	220		2,340
3/26	157	1,940	7 6	26 7	202	50	140	200		2,260
3/27	156	2,180	8 4	29 3		50	140	200		2,260
3/28	157	1,760	6 0	13 1	190	50	140	200		2,260
3/29	157	2,230	6 7	25 5		50	140	200		2,260
3/30	157	1,425	6 3	32 0		50	140	200		2,260
3/31	156	1,140	4 9	9 1	180	50	140	200	100 Subst	2,260
4/ 1	158	2,340	8 6	30 7		50	140	200	100 Subst	2,260
4/ 2	159	1,500	6 1	11 0	200	50	140	200	100 Subst	2,260
4/ 3	159	1,500	4 6	15 0		50	140	200	100 Subst	2,260
4/ 4	159	2,260	5 9	32 1	196	50	140	150		2,060
4/ 5	158	2,380	6 8	48 9		50	140	150		2,060
4/ 6	158	2,580	7 9	50 6		50	140	150		2,060
4/ 7	158	1,970	8 4	55 7		50	140	150		2,060
4/ 8	157	2,850	7 2	20 9	192	50	140	150		2,060
4/ 9	158	2,570	4 0	7 8		50	140	150		2,060
4/10	157	2,045	7 0	28 2	182	50	100	150		1,700
4/11	157	2,260	8 4	50 5		50	100	150		1,700
4/12	157	1,930	5 6	37 3	188	50	100	150		1,700
4/13	157	2,405	9 1	44 3		60	100	100		1,540
4/14	157	1,740	7 6	34 4	216	60	100	100		1,540
4/15	157	2,285	9 1	23 6		60	100	100		1,540
4/16	157	1,780	7 6	39 3		60	100	100		1,540
4/17	157	1,985	8 5	19 2		60	100	100		1,540
4/18	157	2,395	7 1	12 2		60	100	50		1,340
4/19	157	2,085		24 8	186	60	100	50		1,340
4/20	157	2,430	8 6	15 0		60	100	50		1,340
4/21	157	2,200	11 0	10 1		60	100	50		1,340
4/22	158	1,575	7 6	5 0		60	100	50		1,340
4/23	158	1,625	6 5	5 4		60	100	50		1,340
4/24	156	1,695	9 8	7 8		60	100	50		1,340
4/25	156	2,280	10 3	13 7	154	60	100	50		1,340

the diabetic condition, as judged by the excretion of urinary sugar and by blood sugar, became as satisfactory as it was previous to the feeding of the artichokes. This upset may have been, and probably was, merely coincidental to the artichoke regimen, although the long continued strain on the pancreas resulting from the high carbohydrate diet may in itself be sufficient to account for it.

In A. R. (table 4), no change in the excretion of dextrose prevailed when artichoke carbohydrate was substituted in the diet. On the other hand, when artichokes were added to the diet, the urine became sugar-free and remained so, even when the addition of artichoke carbohydrate reached 100 Gm. The conclusion that artichokes in the diet of the diabetic patient have a beneficial effect might easily be drawn from this latter observation. If we had stopped our study at this point, we should have been forced to make such an interpretation of our results. However, in this case an examination of our data shows that such an assumption would be unwarranted, for, when the artichokes were omitted from the diet and were replaced by 100 Gm of other carbohydrate, there was still no glycosuria, showing that the tolerance for dextrose had increased during this period. In fact, the urine was sugar-free even after the diet had reached 200 Gm of carbohydrate, 50 Gm of protein and 150 Gm of fat. The enthusiastic reports that we have received from physicians concerning the therapeutic value of artichokes in diabetes are probably based on experiences similar to this one of ours, in which artichokes were used before the patient's tolerance to carbohydrate had been established. Our experience with this patient offers a striking example of how erroneous such conclusions may be. Further studies on this patient, after the tolerance had been established, gave no evidence that the artichokes had therapeutic value. When artichoke carbohydrate was added to the diet of higher carbohydrate content, both the urinary sugar and the blood sugar increased. The urine again became sugar-free when the diet was reduced to 100 Gm of carbohydrate, 50 Gm of protein and 125 Gm of fat, which was enough to satisfy the patient's appetite and make her comfortable, as she had had intense abdominal distress during the period of heavier feeding. When 25 Gm of flakes (13 Gm of artichoke carbohydrate) was given at 10 a. m. and 3 p. m., respectively, she again complained of the severe formation of gas, and sugar appeared in the urine, but disappeared when the artichokes were omitted. Thus, this case offers no support to the claims that the carbohydrate of the artichoke is better utilized by the diabetic patient than that of other sources.

In patient C. J. (table 5), there was little change in the glycosuria until the last few days of the first period of substitution when 100 Gm of artichoke carbohydrate was fed. Then there was a slight reduction in

the amount of sugar excreted. During the subsequent four day period in which there were no artichokes in the diet, there was a marked average increase in the glycosuria. Later, when artichoke carbohydrate was added to the diet, a decrease in the urinary sugar again occurred, even though the intake of carbohydrate had been increased. On substituting an equivalent amount of other carbohydrate for that contained in the added artichoke, there resulted a moderate average increase in the excretion of dextrose, which continued even after the extra carbohydrate had been omitted and the intake of carbohydrate had been returned thereby to its former level. When 100 Gm of artichoke carbohydrate was again substituted in this diet, the excretion of dextrose decreased somewhat. After the removal of the artichokes from the diet, there was an increase in the amount of sugar elimination, in spite of the fact that the intake of carbohydrate was at the same time decreased. Thus, it is apparent that there has been a lowered excretion of sugar in each period of the feeding of artichokes, with a subsequent increase in the output of dextrose when the artichokes have been withdrawn. We feel that it would be entirely unwarranted to claim without reservation that this was the result of greater tolerance to the carbohydrate of the artichoke, or to some beneficial effect of the artichoke whereby the carbohydrate is better metabolized. Throughout the entire time that the artichokes were fed, this patient complained of abdominal distress, which was undoubtedly due to excessive fermentation, an occurrence that is rather common when the artichokes are first eaten, as has already been mentioned. This would result in a decrease of the assimilable carbohydrate sufficient to account for the fall in the amount of urinary dextrose which was found when artichokes were fed. That there has been no real increase of tolerance to carbohydrate in this patient is further supported by the fact that an increase in blood sugar followed the addition of artichokes to the diet and continued until the intake of carbohydrate was markedly decreased in the latter part of the experimental period. At the end of the experimental period, it was necessary to reduce the intake of carbohydrate much below that given earlier before the elimination of sugar could be reduced to the same low level that originally prevailed. To say that this decreased tolerance was due to the previous feeding of artichokes would be just as unwarranted as to claim that the artichokes had a beneficial effect when they were first fed. The only fair interpretation to make of our data in this case is that the artichoke proved of no value other than to provide variety to the diet.

Thus, if our interpretation of results is correct, the carbohydrate of the artichoke was not utilized any better by our patients than was carbohydrate from other sources, and no evidence was obtained to

indicate that the artichokes contained any insulin-like constituent that would promote the metabolism of carbohydrate

Our results do not conflict with the observations of Root and Baker⁶ and of Carpenter and Root⁷ concerning the utilization and metabolism of carbohydrates from Jerusalem artichokes. To be sure, we did not make an examination of the feces for unabsorbed carbohydrate or study the respiratory exchange to determine the comparative metabolism of carbohydrate during the periods of artichoke feeding. However, the fact that there was no marked reduction in the excretion of sugar when 100 Gm of artichoke carbohydrate was substituted in the diet indicates definitely that a large part of the carbohydrates was absorbed and utilized by our patients.

Our data show that Jerusalem artichokes may be eaten in moderation by patients with diabetes mellitus without causing an increase in the excretion of dextrose when glycosuria is present. We feel justified in the further assumption, based on *a priori* reasoning, that moderate amounts of artichokes may be eaten without producing glycosuria in patients in whom the urine has remained sugar-free. Furthermore, our inquiries have elicited the information that permission to eat Jerusalem artichokes is welcomed and appreciated by patients with diabetes mellitus for the reason that the additional vegetable provides greater variety to the necessarily limited diet of the diabetic person.

CONCLUSIONS

1 The carbohydrates of the Jerusalem artichoke are absorbed and utilized by patients with diabetes mellitus of the mild to moderate type, but they are no better tolerated than carbohydrates from other sources.

2 Whenever we have obtained an apparent beneficial effect from feeding artichokes, there has also occurred a formation of large amounts of intestinal gas arising from bacterial fermentation. Consequently, there must have been a simultaneous reduction in the amount of assimilable carbohydrate sufficient to account for the decrease in the amount of sugar eliminated.

3 We believe that the reputed therapeutic value of Jerusalem artichokes in the diet of the diabetic patient, reported frequently by physicians from their personal experience, is based too often on uncontrolled observations, and is a result both of overenthusiasm on the part of the observer and of the tendency of human nature to anticipate results, even at the expense of erroneous conclusions.

4 As moderate amounts of Jerusalem artichokes may be given without harm to patients with diabetes mellitus, physicians may well adopt the practice of using this vegetable to furnish variety to their prescribed diabetic diets.

EFFECTS OF TREATMENT WITH OXYGEN IN CARDIAC FAILURE*

ALVAN L BARACH, M D

AND

DICKINSON W RICHARDS, JR, M D,

NEW YORK

A state of deficiency of oxygen in the blood, or anoxemia, may be produced by diminishing the concentration of oxygen in the air breathed, or, as is usual in clinical disease, through an impairment of the functional activity of the respiratory or circulatory system. An adequate transportation of oxygen from the lungs to the tissues is maintained by the normal heart. In cardiac disease an impairment of this function exists, although the significance of this type of anoxemia in the symptomatology of cardiac failure is not clearly understood.

HISTORICAL SURVEY

Various aspects of the factor of the deficiency of oxygen in the blood in the production of the symptoms of cardiac failure have been under investigation for the past two decades. In 1915, Means and Newburgh¹ found a diminished oxygen saturation in the venous blood in cases of cardiac insufficiency. Their results were confirmed in a larger number of cases by Lundsgaard². Of considerable interest was Harrop's discovery³ in 1919 that the oxygen saturation of arterial blood was also diminished in cardiac decompensation. These obser-

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* From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital

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¹ A preliminary report of this investigation appeared in the Proceedings of the Society for Experimental Biology and Medicine (27:308 [Jan] 1930)

1 Means, J. H., and Newburgh, L. H. Studies of the Blood Flow by the Method of Krogh and Lindhard, *Tr. A. Am. Physicians* **30**: 51, 1915

2 Lundsgaard, C. Studies of Oxygen in the Venous Blood. II. Oxygen Unsaturation in the Venous Blood of a Group of Patients with Circulatory Disturbances, *J. Exper. Med.* **27**: 179, 1918

3 Harrop, G. A. The Oxygen and Carbon Dioxide Content of Arterial and of Venous Blood in Normal Individuals and in Patients with Anemia and Heart Disease, *J. Exper. Med.* **30**: 241, 1919

vations were later confirmed by Barach and Woodwell,⁴ and by Campbell, Hunt and Poulton.⁵

In 1913, Lewis, Ryffel, Wolf, Cotton and Barcroft,⁶ by using the value K of Hill's equation, reached the conclusion that an increase in the fixed acid of the blood occurred in decompensation of the heart. These observations have been extended by Meakins and Long,⁷ who found an actual increase in the lactic acid of the blood.

The position of the carbon dioxide dissociation curve in cases of cardiac insufficiency is modified by emphysema, renal disease and other conditions, but most investigation has shown that it is either normal or lowered. Beddard and Pembrey⁸ observed a reduction in the alveolar carbon dioxide in cardiac decompensation. Fitzgerald,⁹ and later Porges, Leimdorfer and Marcovici,¹⁰ showed that the alveolar carbon dioxide was low in patients having cardiac disease with dyspnea and normal in those without dyspnea. Peabody¹¹ found that the lowered alveolar carbon dioxide during the period of decompensation was followed by a rise when compensation was restored.

The relation between the alveolar and the arterial carbon dioxide tensions was studied by Peters and Barr,¹² who found that the alveolar values were decidedly lower than the arterial in cases of advanced decompensation. The same observation was noted by Campbell and

4 Barach, A. L., and Woodwell, M. N. Studies in Oxygen Therapy with Determination of Blood Gases. I. In Cardiac Insufficiency and Related Conditions, *Arch. Int. Med.* **28** 367 (Oct.) 1921.

5 Campbell, J. M. H., Hunt, G. H., and Poulton, E. P. An Examination of the Blood Gases and Respiration in Disease, *J. Path. & Bact.* **26** 234, 1923.

6 Lewis, T., Ryffel, J. H., Wolf, C. G. L., Cotton, T., and Barcroft, J. Observations Relating to Dyspnea in Cardiac and Renal Patients, *Heart* **5** 45, 1913.

7 Meakins, J., and Long, C. N. H. Oxygen Consumption, Oxygen Debt, and Lactic Acid in Circulatory Failure, *J. Clin. Investigation* **4** 273, 1927.

8 Beddard, A. P., and Pembrey, M. S. Observations on Pulmonary Ventilation in Disease, *Brit. M. J.* **2** 580, 1908.

9 Fitzgerald, M. P. The Alveolar Carbonic Acid Pressure in Diseases of the Blood and in Diseases of the Respiratory and Circulatory Systems, *J. Path. & Bact.* **14** 328, 1909-1910.

10 Porges, O., Leimdorfer, A., and Marcovici, E. Ueber die Kohlensäurespannung des Blutes in pathologischen Zuständen, *Ztschr. f. klin. Med.* **77** 446, 1913.

11 Peabody, F. W. Studies on Acidosis and Dyspnea in Renal and Cardiac Disease, *Arch. Int. Med.* **14** 236 (Aug.) 1914.

12 Peters, J. P., Jr., and Barr, D. P. Carbon Dioxide Curve and Carbon Dioxide Tension of Blood in Cardiac Dyspnea, *J. Biol. Chem.* **45** 537, 1921.

Poulton,¹³ DAutrebande, Fetter and Meakins¹⁴ later showed that the use of arterial rather than venous blood for the construction of the carbon dioxide curves reduced this discrepancy to a great extent in cases of moderate decompensation

The carbon dioxide dissociation curves of the blood were found by Peters and Barr¹² to be at normal levels in mild or moderate cases of cardiac insufficiency, but definitely reduced in certain cases of advanced cardiac failure, particularly those with marked cyanosis

The hydrogen ion concentration of the arterial blood in cardiac disease may be altered by associated pulmonary or renal disease, by the administration of morphine and by other complicating factors. In general, it has been reported to be within normal limits in mild or moderate degrees of cardiac failure and to be definitely acid in extreme failure, with return to normal when compensation was restored (Peters and Barr¹²). Instances of an alkaline p_H in a few cases of cardiac dyspnea have been reported by Meakins,¹⁴ and by Campbell, Hunt and Poulton.⁵ Fraser, Ross and Dreyer¹⁵ reported nine cases of alkalemia in patients with severe cardiac failure, their method of determining the p_H , however, was the Dale-Evans dialysis technic, and, as no account was taken of the Donnan effect, the accuracy of their results may be questioned

In 1908, Beddard and Pembrey⁸ observed that the inhalation of oxygen resulted in decreased pulmonary ventilation in a patient with cardiac insufficiency. This observation was later reported by Campbell and Poulton,¹⁶ who also observed a corresponding increase in the carbon dioxide concentration of the expired air. It is interesting to note that in normal animals living in an atmosphere containing a high degree of oxygen, J. A. Campbell¹⁷ noted an increase in the tissue tensions of both oxygen and carbon dioxide.

In 1921, Barach and Woodwell⁴ studied the effects of the inhalation of from 40 to 60 per cent oxygen mixtures over periods of from two to four hours in patients with cardiac insufficiency. They found that the arterial anoxemia was relieved, the oxygen saturation of

13 Campbell, J. M. H., and Poulton, E. P. The Relation of Oxygen Hemoglobin to the CO_2 of the Blood, *J. Physiol.* **54** 152 and 166, 1920-1921

14 DAutrebande, L., Fetter, W. J., and Meakins, J. C. Influence of Circulatory Disturbances on Gaseous Exchange of Blood, *Blood Gases and Circulation Rate in Cases of Mitral Stenosis*, *Heart* **10** 153, 1923

15 Fraser, F. R., Ross, J. P., and Dreyer, N. B. Reaction of Blood in Relation to Dyspnoea, *Quart. J. Med.* **15** 195, 1922

16 Campbell, J. M. H., and Poulton, E. P. The Effect on Breathless Subjects of Residence in an Oxygen Chamber, *Quart. J. Med.* **20** 141, 1926-1927

17 Campbell, J. A. Prolonged Alterations of Oxygen Pressure in the Inspired Air with Special Reference to Tissue Oxygen Tension, Tissue Carbon Dioxide Tension and Haemoglobin, *J. Physiol.* **62** 211, 1927

arterial blood being elevated to, or near, the normal level. An increase in the oxygen saturation of venous blood also occurred, apparently proportional to the change in that of arterial blood. The outstanding, objective, clinical results were a diminution of the cyanosis and a slowing of the pulse rate. In some cases a distinct increase in the carbon dioxide content of the arterial and venous blood took place. In two instances of right bundle branch block, a decreased notching and a diminished height of the R wave were present during the inhalation of oxygen.

Recently, Baker¹⁸ reported a case of bundle branch block in which the inhalation of oxygen resulted in a disappearance of the aberrant ventricular complexes and a striking improvement in intraventricular conductivity.

In most of the previous studies the obvious difficulty in determining the effect of oxygen therapy in cardiac disease has been a technical one, in that it was not possible to keep patients continuously in atmospheres containing a high degree of oxygen over considerable periods of time. This hindrance has been overcome by the use of an oxygen chamber in which the patient may reside in an atmosphere containing 45 per cent oxygen in comfort for weeks or months at a time.

METHODS

In the present investigation, throughout which the Barach oxygen chamber was used, we studied eight patients who were suffering from various forms of circulatory failure.

The method of study varied considerably in detail according to the clinical situation. The general plan was as follows. The patient was first given the benefit of treatment in the ward for a number of days (see clinical histories), with digitalis and other treatment as indicated. At a time when his condition either appeared to be stationary or was becoming worse, he was transferred to the oxygen room. In certain cases an additional control period was carried out in the oxygen room, in which the temperature was maintained at 66 degrees, the relative humidity at 40 per cent and the oxygen concentration at 21 per cent. The concentration of oxygen in the chamber was then raised to 45 per cent, and the patient was kept in this atmosphere for from three to sixty days.

After a number of days in an atmosphere containing a high degree of oxygen, and when, clinically, the patient's condition seemed to be changing little from one day to the next, the concentration was lowered to 21 per cent and maintained at this level for three or four days, with the patient remaining in the chamber. This was done expressly to rule out the possibility that the changes that were observed in the patient's condition during residence in the oxygen chamber were simply due to the alteration in temperature and humidity from those in the ward. Usually he was given a high amount of oxygen for a further period, after which the concentration was lowered gradually over a day or two, the patient was then returned to the ward. Sometimes it was necessary to give the patient further treatment with oxygen by nasal catheter.

¹⁸ Baker, B. M. The Effect of Cardiac Rate and the Inhalation of Oxygen on Transient Bundle Branch Block. *Arch Int Med* 45:814 (May) 1930.

The Barach oxygen chamber has been described elsewhere¹⁹ The ventilation is by thermal circulation of the air The temperature can generally be kept constant within 2 degrees, in this investigation for most of the time it was between 64 and 66 degrees, the humidity was regulated between 35 and 40 per cent The oxygen concentration was maintained at 45 per cent, with a range of 2 or 3 per cent The carbon dioxide concentration varied between 0.15 and 0.5 per cent

All of the patients (except I S, case 8) were given a measured intake of fluids and a "cardiac diet" (limited amount of fluids, low in salt, with small, frequent feedings), and their output of urine was measured The administration of digitalis, sedatives and other treatment was kept, as far as possible, the same when the patient was in an atmosphere containing a high degree of oxygen as during the control periods No diuretics were given at any time during the period of observation

Determinations of the basal metabolic rate were made with the Benedict-Roth apparatus Ventilation was calculated from the graphic records of the respiration obtained with this apparatus, except in cases 3 (J Sn), 7 (A S) and 8 (I S), in which the expired air was collected in a Douglas bag

Studies of the blood were made on arterial samples that were drawn in the morning under basal conditions from the brachial (occasionally the radial) artery For determinations of the oxygen and carbon dioxide, blood was transferred under oil to containers with small amounts of dried neutral potassium oxalate and sodium fluoride In the construction of carbon dioxide curves of oxygenated whole blood, sometimes two points were determined, sometimes only one, in which latter case the slope was estimated from the oxygen capacity (see Peters, Bulger and Eisenman,²⁰ and Richards and Strauss²¹) The Van Slyke-Neill manometric apparatus was used for measurements of gas in the blood, and the Boothby modification of the Haldane apparatus for the analyses of gas A correction was made in the carbon dioxide values of the blood after equilibration in the tonometers, owing to loss of carbon dioxide capacity during this procedure²² Arterial p_H values were calculated from the carbon dioxide content of arterial whole blood and from the carbon dioxide curves, the graphic method described by Van Slyke and Sendroy²³ being used In the determination of the cardiac output in cases 6 (J Sr), 7 (A S), 3 (J Sn) and 8 (I S), the Fick principle was employed with carbon dioxide from arterial blood as measured, and the carbon dioxide content of mixed venous blood obtained by a technic previously described by Richards and Strauss²¹ The output of carbon dioxide was found by collecting expired air in a Douglas bag and analyzing for carbon dioxide

19 Barach, A L A New Type of Oxygen Chamber, *J Clin Investigation* 2:463 (Aug 20) 1926, New Oxygen Chamber Ventilated by Thermal Circulation of Air, *Mod Hosp* 32 144 (Jan) 1929

20 Peters, J P, Bulger, H A, and Eisenman, A J Studies of Carbon Dioxide Absorption IV *J Biol Chem* 58 747, 1923

21 Richards, D W, and Strauss, M L Circulatory Adjustment in Anemia, *J Clin Investigation* 5 161, 1928

22 Bock, A V, Dill, D B, Edwards, H T, Henderson, L J, and Talbott, J H On Partial Pressures of Oxygen and Carbon Dioxide in Arterial Blood and Alveolar Air, *J Physiol* 68 277, 1929

23 Van Slyke, D P, and Sendroy, J, Jr Studies of Gas and Electrolyte Equilibria in Blood Line Charts for Graphic Calculation by Henderson-Hasselbalch Equation and for Calculation of Plasma Carbon Dioxide Content from Whole Blood Content, *J Biol Chem* 79 781, 1928

RESULTS

Of the eight cases studied, six were primarily of cardiac disease, the remaining two primarily of pulmonary disease with secondary circulatory failure. The effects on these patients of continuous residence in atmospheres containing a high degree of oxygen are shown in the clinical histories and in the accompanying tables and charts.

It will be noted that the most consistent and pronounced effects were obtained in the following three patients, all of whom had marked congestive cardiac failure: case 1, A L, a 55 year old Negress, with cardiac insufficiency based on myocardial fibrosis and general arteriosclerosis, case 2, J McQ, a man of 53 years, with cardiac insufficiency, together with a large aortic aneurysm, and case 3, J Sn, a man of 30 years, with cardiac insufficiency associated with advanced fibrosis of the lung.

In these patients the major effects of the inhalation of an atmosphere containing 45 per cent oxygen were: 1. There were marked subjective improvement, decrease of cyanosis, relief of dyspnea, orthopnea and cough, beginning generally within three hours after the entrance of the patients into an atmosphere containing a high degree of oxygen. 2. There was an increase of urinary output and disappearance of edema of gradual onset which usually did not reach its maximum for from three to five days. In (case 3) J Sn, the diuresis was paralleled by a marked loss in weight. In the other two cases the weight was not measured. In all three patients a return to an atmosphere containing a normal amount of oxygen resulted in a decreased urinary output and a return of edema. When the oxygen concentration was again raised a second diuresis was brought about. In cases 1 (A L) and 2 (J McQ) this sequence was obtained both by transferring the patient from the oxygen room to the ward, and by lowering and raising the oxygen in the chamber without removing the patient from it. In J Sn, this course could not be followed, but at a later time the same result was obtained while the patient was in the ward, the administration of oxygen by nasal catheter was stopped, and it was then resumed after the patient had shown definite signs of the retention of water (decreased output and increased weight).

3. There was increased oxygen saturation of arterial blood. This was definite and marked for A L (case 1) and J Sn (case 3), as shown in the tables. In case 2 (J McQ), unfortunately, the earlier measurements of arterial oxygen were vitiated by the fact that a determination of the basal metabolic rate (a very high degree of oxygen being used for rebreathing) was performed just before the arterial puncture, and sufficient time was not allowed for the patient's arterial blood to return

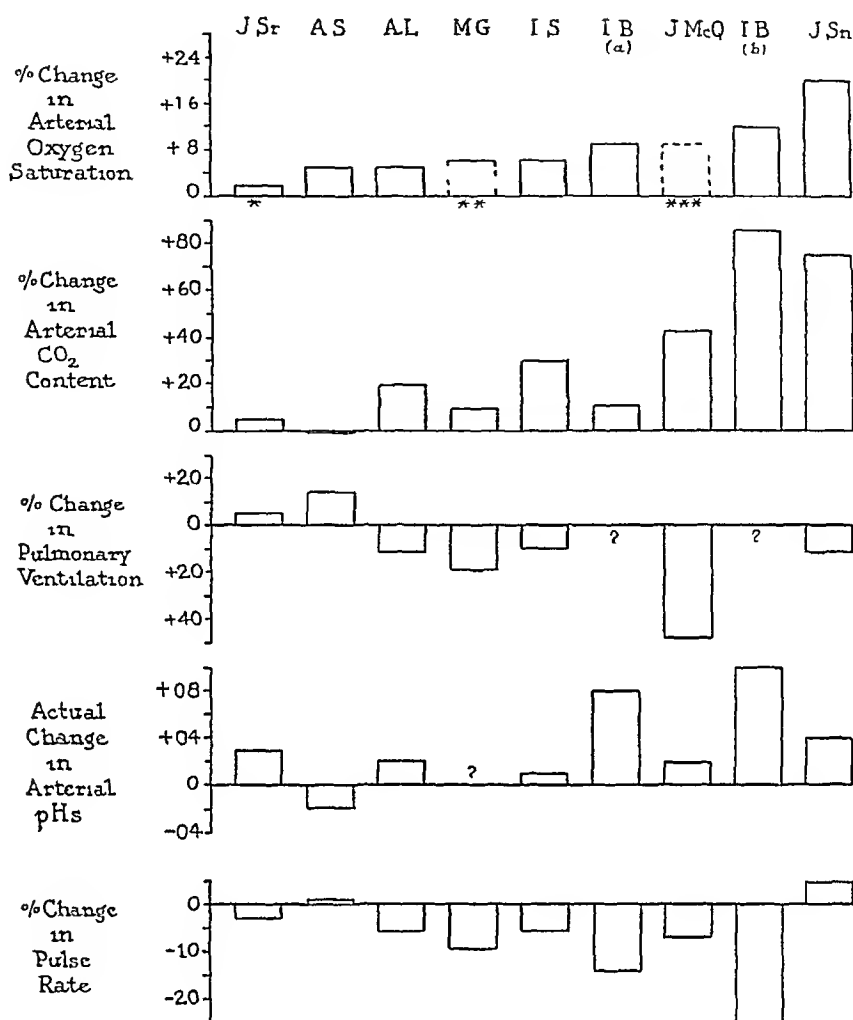


Chart 1—Changes in the oxygen saturation of arterial blood, in the carbon dioxide content of arterial blood, in pulmonary ventilation, in arterial p_H and in pulse rate, following the residence of the patients in an atmosphere containing a high degree (45 per cent) of oxygen. The initials represent the individual patients. Patient I B (case 5) was studied over two periods: (a) from September 27 to October 12, and (b) from October 15 to October 19. Table gives further details.

The oxygen saturation of arterial blood while the patient was residing in an atmosphere containing 45 per cent oxygen was not measured, but it was normal even when the atmosphere contained but 21 per cent oxygen. ^{*} An estimate, based on the facts that (a) clinical cyanosis was always marked but not extreme, (b) little observable change occurred while the patient was in an atmosphere that contained 45 per cent oxygen and (c) the oxygen saturation of arterial blood under the conditions just mentioned was only 87 per cent. ^{**} An estimate, based on the facts that (a) oxygen saturation of arterial blood while the patient was in the ward, in a state of decompensation, was 84 per cent, and that (b) clinically, cyanosis cleared completely while he was in an atmosphere that contained 45 per cent oxygen.

TABLE 1.—Circulatory and Respiratory Changes with Varying Oxygen Concentrations of Inspired Air *

Case	Date	Per Cent of Oxygen in Atmosphere	Arterial Oxygen Content, per Cent by Volume	Arterial Oxygen Capacity, per Cent by Volume	Per Cent of Oxygen Saturation of Arterial Blood	Dioxide Content per Cent by Volume	Arterial Carbon Dioxide Tension, mm	Carbon Dioxide or Arterial Blood at 40 mm	Arterial <i>p_a</i>	Ventilation, Liters per Minute	Average Vital Capacity, Liters	Basal Metabolic Rate	Average Pulse Rate	Average Respiratory Rate	Average Temperature	Average Systolic Pressure	Average Diastolic Pressure	Cardiac Output of Liters per Minute
A L	July 6	45	18.0	18.7	96	53.1	10.7	47.1	7.45	7.2	0.6	+1.2	60	21	98.6	115	65	
	Aug 16	25	17.8	19.5	76	45.0	36.0	47.1	7.4	7.7	0.6	+1.2	66	21	98.6	121	69	
	Aug 16	21				40.9				11.8	0.6	+1.2	84	15	99.3	129	56	
	Aug 22	45								7.5	2.4	+1.2	76	15	98.6	115	54	
J MeQ	Sept 30	35				58.3	41.0	57.7	7.48	6.2	2.2	+1.2	53	14	98.8	120	40	
	Sept 25	35				56.1	40.6	55.5	7.46	6.3	2.0	+1.2	52	17	99.2	120	40	
	Oct 5	21				50.3	36.2	51.7	7.47	6.6	2.2	+1.2	72	19	99.2	120	40	
	Oct 5	21				54.4	32.1	10.6	7.12	11.7	1.0	+1.2	100	25	101.1	105	87	
J Sn I	Dec 23	21	16.6	23.9	70	38.4	50.6	61.5	7.44	10.0	0.8		116	22	101.0	120	81	1.1
	Jan 2	45	16.2	18.4	90	69.9	50.0	61.5	7.48	10.0	0.8		116	22	101.0	124	80	1.8
	Jan 6	45	16.5	17.8	94	56.8	50.6	61.5	7.44	10.0	1.1		110	22	100.4	110	82	
	Jan 19	25†	16.0	18.4	87	52.7				10.6	1.6		106	21	99.6	114	90	
M G	Mar 6	25†	16.9	19.7	86	48.9				10.6	2.1		106	21	99.8	112	70	
	Mar 27	21	17.7	18.0	65	44.6				10.5	1.0		116	24	100.4	112	70	
	Sept 29	21	16.9			48.7	38.5	48.8	7.42	8.5	1.5	+1.7	88	21	100.4	100	85	
	Oct 12	45	17.3	19.0	87	48.7				8.5	1.6	+6	80	24	99.8	135	85	
I B	Sept 27	21	19.3	23.0	84	37.2	35.2	43.9	7.44	8.5	1.3		92	24	100.2	130	80	
	Oct 12	45	22.8	24.4	93	41.2	25.2	33.9	7.36	7.7	1.2		77	27	100.2	100	7	
	Oct 15	25†	19.7	23.5	84	26.4	38.0	50.9	7.46	10.6	3.5		106	35	101.4	90	7	
	Oct 15	25†	21.3	21.8	98 (?)	49.0				80	27		80	27	99.8	118	78	
J Sr	July 23	21	18.3	20.4	91	44.0	32.0	50.5	7.50	12.3	3.3	+9	74	24	98.8	106	77	
	July 29	21	20.9	21.6	97	46.2	34.0	46.9	7.45	9.3	3.3	+2	70	25	98.8	106	77	3.2
	Aug 6	21	20.9	21.0	95	43.4	32.2	50.6	7.51	11.1	3.0	+10	72	24	98.2	119	80	
	Aug 13	45	20.8			46.1	32.2	50.6	7.51	11.6	2.6	+7	70	24	98.8	126	85	3.5
A S	Mar 23	21								11.3	2.8		68	22	98.6	100	60	
	Mar 13	21	20.3	31.7	61					9.5	2.1		95	21	99.8	100	60	
	Mar 18	21	18.5	33.8	55	34.2	32.0	39.7	7.48	9.4	2.0		100	21	100.0	90	60	1.9
	Mar 28	21	20.2	33.8	60	38.6	35.0	39.2	7.46	10.5	2.5		85	20	99.8	100	60	2.2
I S	April 1	45	21.5	33.2	65	40.0	48.0	50.3	7.39	7.2	1.1		86	20	99.5	130	100	3.0
	May 2	21	17.8	20.3	88	51.9	61.3	61.1	7.40	9.0	1.2		102	22	99.2	128	98	
	May 22	45	18.2	19.4	94	72.1	67.0	61.5	7.37	6.5	1.0		90	25	99.5	102	102	3.2
	June 25	45	16.7	18.0	93	73.5							85	24				

* All chemical data reported in this table were obtained from arterial blood

† Other measurements of the blood of this patient were as follows on December 28, lactic acid, 22.6 mg per hundred cubic centimeters, serum chlorine, 97 mm serum protein, 6.14 per cent, on January 2, serum chlorine, 95.8 mm, serum protein, 5.05 per cent, on January 6, lactic acid, 7 mg per hundred cubic centimeters, serum chlorine, 97 mm, and serum protein, 5.35 per cent

‡ Patient was receiving oxygen by nasal catheter

to its usual oxygen saturation. Clinically, the clearing of this patient's cyanosis when he was in an atmosphere containing a high degree of oxygen was definite.

4 There was a sharp rise in the carbon dioxide content and in the carbon dioxide curve of arterial blood when the patient was in an atmosphere containing a high degree of oxygen.

5 There was decreased pulmonary ventilation, lowered pulse rate and moderate increase in the vital capacity of the lungs.

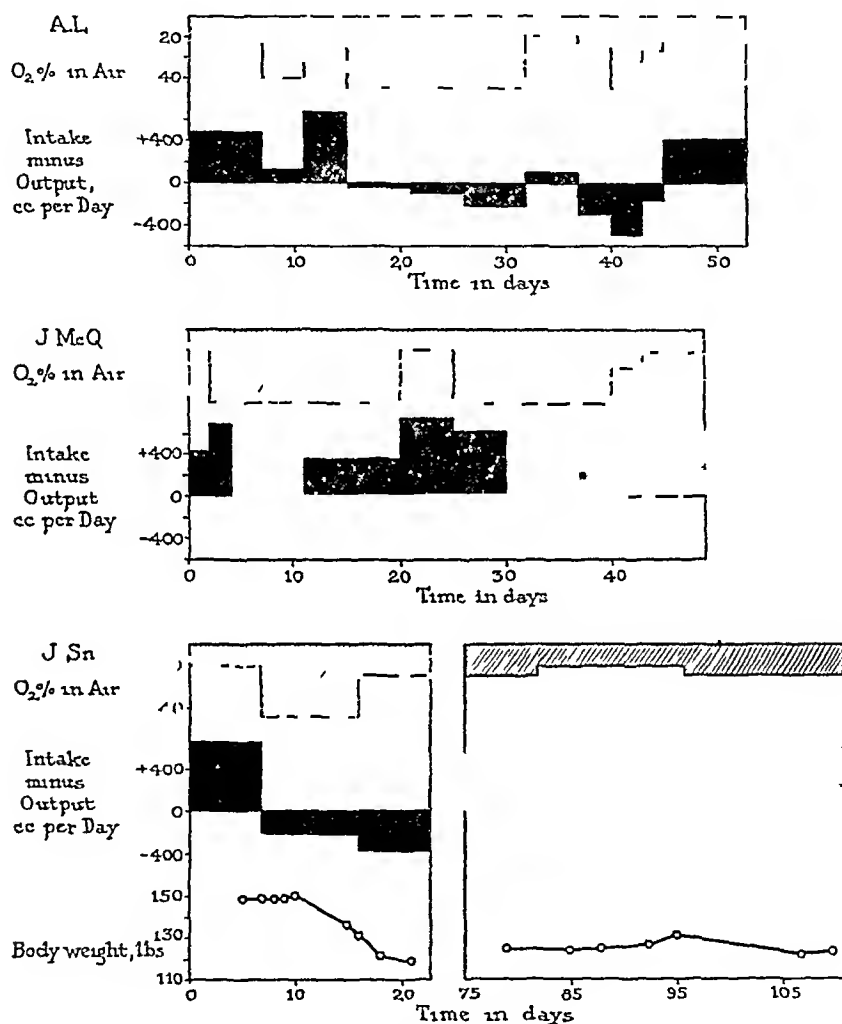


Chart 2—Relation of the oxygen in the atmosphere to the balance of water in patients A L, J McQ and J Sn (cases 1, 2 and 3). The upper (shaded) blocks show the percentage of oxygen in the atmospheric air, the lower (solid) blocks, the total intake of fluids minus the urinary output, the differences expressed as cubic centimeters per day.

6 In case 3 (J Sn) other measurements showed (a) a slight increase in cardiac output, (b) a sharp fall in the lactic acid of the blood, from 22.6 mg to a normal value of 7 mg and (c) a lowered percentage of protein in the serum. An unexplained, profuse, intestinal hemorrhage, with considerable fall in the oxygen capacity, was probably concerned in this last change, owing to dilution of the blood serum.

M G (case 4) and I B (case 5) clearly represent a different group from the three first summarized. These were both cases of advanced and active rheumatic cardiac disease, with cyanosis, generalized passive congestion, edema and irregular fever. Subjectively, the patients were more comfortable and less dyspneic when they were in an atmosphere containing a high degree of oxygen, their cyanosis was somewhat improved, and in one case comparative measurements showed an increase in the arterial oxygen saturation from 84 to 93 per cent. In each case there was a moderate rise in the level of the carbon dioxide curve. Little change, however, occurred in the edema, and there was no tendency to diuresis. However, I B (case 5) was removed abruptly from the chamber when the atmosphere contained 45 per cent oxygen to the ward, where she rapidly went into collapse, with renal suppression for twenty hours, low blood pressure and profound cyanosis. The arterial oxygen saturation again fell to 84 per cent (this measurement was taken when the patient was receiving 4 liters of oxygen a minute by nasal catheter), the carbon dioxide dropped to the remarkably low value of 26.4 per cent by volume, and the arterial p_H fell from 7.44 to 7.36. After the patient returned to the chamber in which the atmosphere contained 45 per cent oxygen, as noted in the clinical record, she quickly returned to her former condition. During the next twenty-four hours she passed 1,000 cc of urine. Both of these patients showed lowered pulse rates while they were in an atmosphere containing a high degree of oxygen.

In the five cases cited, all of the patients may be said to have improved in an atmosphere containing 45 per cent oxygen. Other changes occurred, although not constantly: lowered respiratory rate, lowered body temperature, decreased basal metabolism, slightly raised arterial p_H and decreased red blood cells and hemoglobin. There seemed to be no consistent alteration in the blood pressure.

Two patients J Sr (case 6) and A S (case 7) showed practically no reaction whatever to the increase in atmospheric oxygen. Case 6 was in a man of 54, with long-standing mitral stenosis, great cardiac enlargement and enlargement of the liver, but no edema or orthopnea. Clinically, he was moderately cyanotic, but this was evidently of venous origin, for when he was in the ward his arterial blood showed an oxygen saturation of 91 per cent or more. The development of a mild rhinitis and bronchitis, with a transient lowering of the carbon dioxide curve and of the vital capacity, seemed to be the only change while he was in the oxygen chamber. Subjectively, he was no better.

A S (case 7), a girl, aged 13, had congenital cardiac disease, which autopsy showed to be the tetralogy of Fallot, combined with patent ductus arteriosus. The case is being reported by Richards in further

detail elsewhere²⁴ It is sufficient to note here that the arterial oxygen saturation of about 60 per cent was increased only to 65 per cent when she was in an atmosphere containing a high degree of oxygen, that there was no change in the carbon dioxide or in the urinary output, that the pulmonary blood flow was practically unaltered, and that subjectively she was not improved She did not have edema at any time She was not in the oxygen chamber long enough to rule out the possibility of a change in urinary output relative to the intake of fluid

Finally, I S (case 8), a man, aged 29, with advanced chronic tuberculosis, including cavitation and paralysis of the right side of the diaphragm due to phrenicotomy, was also studied in the oxygen chamber He was moderately cyanotic, markedly dyspneic and orthopneic and suffered greatly from a violent cough On examination, his heart, except for the rapid rate, appeared to be normal For the first six days he was kept in the oxygen chamber with the atmosphere containing 21 per cent of oxygen, then the oxygen was raised to 45 per cent and was maintained at that level for two months Table 1 shows that there were a moderate improvement in the arterial oxygen saturation, an increased urinary output lasting about two weeks (though the patient never had any edema) and a remarkable rise in the carbon dioxide content of the blood of from 54.9 to 73.5 per cent by volume, giving an arterial carbon dioxide tension of 67 mm Subjectively the patient was slightly better in an atmosphere containing a high degree of oxygen

COMMENT

In this somewhat varied group of cases of circulatory failure in which treatment with atmospheres containing 45 per cent oxygen was instituted, there are certain general tendencies that may be summarized

The six patients who showed unmistakable clinical improvement, when breathing room air, were characterized by a low arterial oxygen saturation and a definitely increased saturation when in an atmosphere containing 45 per cent oxygen With one exception, case 9, I S, they had congestive cardiac failure It seemed to be true also that marked subjective benefit came only after the oxygen saturation had been raised to 90 per cent or above Clinically, the clearing of cyanosis in these patients occurred within a few hours after their introduction to the atmosphere containing a high degree of oxygen

Conversely, the two patients whose arterial oxygen (and the cyanosis) was not appreciably altered showed no effects as a result of remaining in an atmosphere containing a high degree of oxygen

²⁴ Richards, D W Congenital Heart Disease Measurement of the Circulation, Arch Int Med 47:484 (March) 1931

TABLE 2—*Intake of Fluid and Output of Urine with Varying Determinations of the Oxygen Concentrations of the Respired Air*

Case and Date	Days*	Ward or Oxygen Room	Per Cent of Oxygen in Atmosphere	Average Intake of Fluids per Day, Cc	Average Output of Urine per Day, Cc	Difference	Weight, Pounds	Average Pulse Rate
A L	7	W	21	1,124	643	+481		74
June-July, 1929	4	O	40	628	495	+133		70
	4	W	25†	1,080	337	+693		80
	6	O	45	972	1,030	-58		64
	5	O	45	968	1,076	-108		62
	6	O	45	927	1,153	-226		60
	5	O	19	656	548	+108		68
	3	O	25	730	1,013	-313		66
	3	O	45	627	1,137	-510		58
	2	O	27	835	1,012	-177		
	8	W	21	1,400	986	+414	108	67
J McQ	2	W	21	900	475	+425		84
August-September, 1929	2	O	45	1,145	150	+695		83
	7	O	45	1,449	1,587	-138		76
	9	O	45	1,272	899	+373		78
	5	O	20	1,263	510	+753		85
	5	O	45	1,250	613	+637		78
	7	O	45	1,267	1,226	+41		74
	3	O	45	1,203	797	+406		70
	3	O	28	1,355	598	+757		72
	6	W	21	1,388	746	+642		76
J Sn	7	W	21	1,349	689	+660	119	108
January-March, 1930	9	O	45	1,253	1,473	-215	137	110
	7	W	25†	1,050	1,436	-386	119	110
	7	W	25†	1,514	946	+568	125	106
	7	W	21	1,393	675	+718	125	112
	7	W	21	1,532	646	+886	130	116
	7	W	25†	1,371	907	+464		90
	8	W	25†	1,297	952	+345	122	114
M G	7	W	21	1,557	454	+1,103	139	86
September-October, 1929	7	O	45	1,531	508	+1,023		76
	7	O	45	1,296	458	+838		80
	10	W	21	1,048	318	+730		100
I B	5	W	21	1,000	550	+450		114
September-October, 1929	1	O	21	1,260	650	+610		92
	5	O	45	1,148	420	+728		79
	5	O	45	1,188	458	+730		82
	6	O	45	1,280	594	+686		77
	1	W	21					106
	1	W-O	21 40	1,105	235	+870		106
	6	O	45	1,240	673	+567		80
	7	O	40	1,291	683	+608		95
	8	W	25†	913	394	+519		85
	8	W	25†	1,088	221	+867		65
J Sr	6	W	21	1,079	1,042	+37	145	74
July-August 1929	3	W-O	21	1,057	833	+224		70
	7	O	20	1,134	1,079	+55		72
	7	O	45	1,276	1,054	+222		70
	7	W	21	1,497	804	+693	145	68
A S	4	W	21	2,500	725+	+1,775		83
April, 1930	4	W	21	2,725	431+	+2,294		85
	4	O	45	2,100	813	+1,287		86
	4	W	21	2,413	493+	+1,920		98
I S	6	O	21	2,154	608	+1,546	100	102
May, 1930	6	O	45	1,421	808	+613	100	84
	6	O	45	1,516	1,071	+445	101	86
	6	O	45	1,483	767	+716	101	90

* The total time during which a patient was studied was divided into short periods of a few days each

† Patient in the ward, receiving oxygen by nasal catheter

All patients who were clinically improved also showed a rise in the arterial carbon dioxide content and in the level of the carbon dioxide dissociation curves. There seemed to be some proportion between the extent of this rise and the increase in the arterial oxygen saturation (chart 1)

It is of interest to inquire whether the aforementioned changes in the gas content of the blood can be correlated with the alterations in pulmonary function that occur with increased oxygen concentration in the respired air

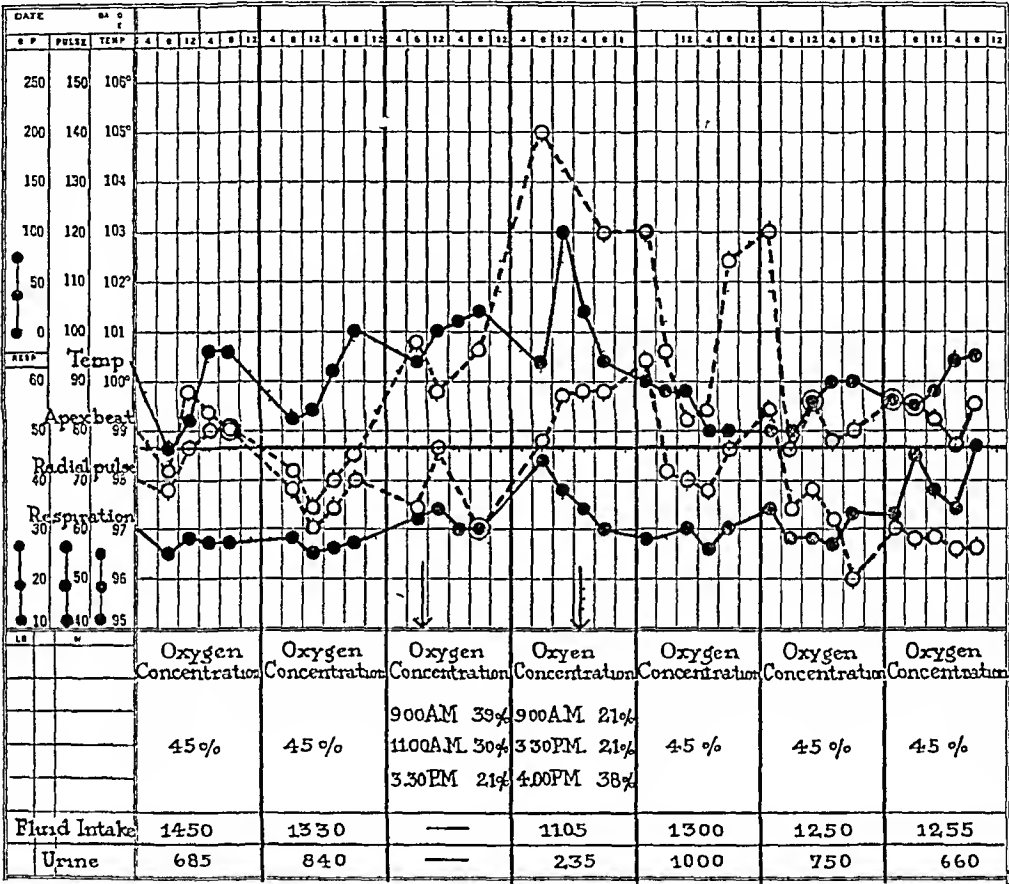


Chart 3 (case 5) —Hospital chart of patient I B, showing changes following her withdrawal from an atmosphere containing a high degree of oxygen for twenty hours

In cases of advanced cardiac failure, the defects in the anatomy and physiology of the lungs have been extensively investigated. The marked decrease in vital capacity has been associated by various writers with the suggestion of von Basch²⁵ that there is a stiffening of the lung (Lungenstarre) due to the congestion of the pulmonary blood vessels. In one of our cases (J Sn) during the stage of advanced congestive

²⁵ von Basch, S S K. Verschiedene Aufsätze im klinische und experimentelle Studien, Berlin, A Hirschwald, 1891

failure, the patient used his full vital capacity at each respiration. In such a situation, an increased ventilation can, of course, occur only by an increased rate of respiration. This phase has been investigated by Engelhard²⁶ and others. It has been shown by Binger²⁷ that the residual air is diminished relatively little in cases of congestive failure. In this condition Siebeck²⁸ has demonstrated the unequal aeration of different parts of the lungs. That there is a decreased capacity of the alveolar membranes for the diffusion of respired gases seems inevitable, but the extent of this effect is unknown.

The end-results of these various aspects of pulmonary dysfunction are dyspnea, with increase in ventilation, and in the advanced stages, more or less arterial oxygen unsaturation. The transport of carbon dioxide by the lungs is less embarrassed, and (as has been described) accumulation of carbon dioxide rarely occurs. The question of the actual nature of the stimulus in the "respiratory center" and the influence of the factors mentioned need not be discussed in the present connection.

It is clear that the chief difficulty in the pulmonary function in cardiac failure, namely, the transport of oxygen from the atmosphere to the blood, will at once be lessened when increased concentrations of this gas are breathed. Pulmonary (and arterial) blood will receive increased oxygen saturation, and at the same time pulmonary ventilation can decrease. As to the internal mechanism whereby the respiratory activity is lessened, our data do not contain anything new. Clearing of arterial anoxemia will presumably decrease the accumulation of acid in the tissues. In the one case in our series in which lactic acid was measured (case 3, J. Sn.), the value rapidly returned to normal following the inhalation of atmosphere containing a high degree of oxygen.

That the respiratory stimulus was generally decreased is evidenced by the lowered ventilation (chart 1), and that there was some diminution in the acidity of the tissues is suggested by the small but consistent lowering of the arterial hydrogen ion concentration.

Considered from the point of view of transport of oxygen and carbon dioxide, the altered pulmonary action resulting from inhalation of a high degree of atmospheric oxygen has in itself a consequence that may be related to the increased carbon dioxide levels of the blood which we have found. The high degree of oxygen in the inspired air will evidently make possible the absorption of a sufficient amount of oxygen at a lower ventilation than previously. But decreased ventilation will in turn make more difficult the necessary elimination of carbon dioxide.

26 Engelhard, A. Der Wert der Spirometrie für die Klinik der Herzkrankheiten, *Deutsche Arch f klin Med* **156** 1 1927.

27 Binger, C. A. L. Lung Volume in Heart Disease, *J Exper Med* **38** 445, 1923.

28 Siebeck, R. Ueber die kardiale Dyspnoe, *Klin Wchnschr* **8** 2121, 1929.

To meet this situation, two adjustments can be made either an increase in pulmonary ventilation or an increase in the carbon dioxide levels of the blood and hence in the alveolar air so that a given amount of carbon dioxide can be eliminated at a lower ventilation than before. It seems that the state of equilibrium which these cases have assumed in an atmosphere containing a high degree of oxygen is of the latter type.

It should also be noted that as cardiac compensation is restored, a rise in the carbon dioxide levels has been observed to take place even in cases in which oxygen therapy was not given, although generally not to the same degree.

The mechanism whereby the rise in the carbon dioxide level actually took place is difficult to explain. The fall in the level of the lactic acid in the blood would be entirely inadequate to account for the total increase in carbon dioxide that we found in several cases. Further studies now in progress indicate that so far as the blood electrolytes are concerned, a rise in the serum bicarbonate is accompanied by a fall in the serum chloride.

One of the important features in the group of cases in which the patients were benefited by obtaining a high degree of oxygen is that clinical improvement continued steadily for a week or more after the patient's first introduction to an atmosphere containing 45 per cent of oxygen. The clearing of cyanosis and some relief in the urgency of the dyspnea began, as noted, within a few hours. Thereafter, the decrease in respiratory discomfort and especially the gradual disappearance of orthopnea were progressive for a number of days.

The most striking of the delayed effects in three cases were the diuresis and the disappearance of edema. Clinical improvement was most marked in these patients, all of whom had extreme congestive cardiac failure. Edema recurred when the oxygen was lowered to 21 per cent if compensation was not fully restored by that time.

For this apparent diuretic effect of an atmosphere containing a high degree of oxygen we are not able to offer an adequate explanation on the basis of the facts now at our disposal. That a better state of the circulation resulted from the improved transportation of oxygen is obvious, and that this must have been reflected in a more adequate renal function appears also to be a necessary inference. Other possibilities suggest themselves: (a) tissue capillaries, dilated because of anoxemia (Krogh²⁹), with consequent alteration in permeability (Landis³⁰).

²⁹ Krogh, A. *The Anatomy and Physiology of Capillaries*, New Haven, Conn., Yale University Press, 1922.

³⁰ Landis, Eugene M. *Micro-Injection Studies of Capillary Permeability*, III. The Effect of Lack of Oxygen on the Permeability of the Capillary Wall to Fluid and to the Plasma Proteins, *Am J Physiol* **83** 528, 1928.

returned to their normal state, (b) increased capillary and venous pressures returned to normal, (c) some other alteration may have taken place in the water balance of the tissues, following exposure to a high degree of oxygen, dependent on the general electrolyte changes of which the rise in the carbon dioxide curve was a part. It is evident that a more complete metabolic study should be made of this type of diuresis.

Our studies of the dynamics of circulation were not sufficiently comprehensive to permit conclusions as to the possible effects of treatment with oxygen in this regard. The difficulty of making satisfactory determinations of cardiac output in cases of cardiac failure is well known, in four cases we were able to make a fairly reliable measurement of this function namely, in the cases of J. Sr and A. S. (who were not improved clinically), J. Sn and I. S. All four showed a small rise in cardiac output following the inhalation of a high degree of oxygen, the change in each case being about at the upper limit of the error of the method. There were no consistent changes in arterial blood pressure. The pulse rate was lowered. Measurements were not made of the blood volume, blood velocity and venous pressure.

SUMMARY

1 Eight patients suffering from various forms of circulatory failure, with cyanosis, were treated in an oxygen chamber for from three to sixty days, the oxygen in the atmosphere being kept at 45 per cent.

2 The five patients who had congestive cardiac failure with arterial anoxemia were benefited by an atmosphere containing a high degree of oxygen. The striking objective changes were increased arterial oxygen saturation with decrease of cyanosis, diminished pulmonary ventilation and rise in the carbon dioxide levels. Subjectively, there was relief from dyspnea and orthopnea.

3 Three of the patients experienced marked diuresis and disappearance of edema while breathing a high degree of oxygen. The edema returned when the degree of oxygen was lowered, and again disappeared when the oxygen was increased, as long as cardiac insufficiency was present.

REPORT OF CASES

CASE 1—*History*—A. L., a colored woman, aged 55, was admitted to the hospital for the sixth time during the past five years on April 29, 1929, with a diagnosis of cardiac insufficiency and hypertrophy, auricular fibrillation, chronic myocarditis and general arteriosclerosis. She was in a severe state of decompensation. Ten days before admission she caught a cold, which was followed by dyspnea, cough, frothy sputum and swelling of the extremities.

Physical Examination—The patient was old-looking, markedly uncomfortable, dyspneic and orthopneic, and had an anxious expression. The heart was greatly enlarged to the left and to the right, fibrillating, with a rate between 90 and 100,

the pulse was very feeble. A loud systolic murmur was heard over the precordium. The blood pressure was 140 systolic and 80 diastolic. Numerous sibilant and a few moist râles were heard over the lungs. The liver was palpable midway to the umbilicus. There was moderate edema of the extremities. The Wassermann reaction of the blood was negative. The blood urea was 0.40 Gm per liter. The excretion of phthalein was 35 per cent in two hours and a quarter.

Course—The patient improved temporarily after phlebotomy and the administration of salyrgan and digitalis. At the end of six weeks' residence in the hospital she was still uncomfortable, with marked dyspnea and epigastric distress. The edema in the legs was increased, while fluid was accumulating in the abdomen and chest. On June 10, she was transferred to the oxygen chamber, in which the atmosphere contained an oxygen concentration of 45 per cent. Striking improvement occurred in her general well-being within three hours and relief from dyspnea within six hours. During the first four days in the oxygen chamber, she was more comfortable and entirely relieved from orthopnea, though the epigastric discomfort persisted. She was then removed from the chamber, and in the next twenty-four hours the pulse rate rose from 70 to 90, the temperature from 99 to 100 F and the rate of respiration from 20 to 38. Dyspnea and orthopnea returned. For part of the time during the next four days she received oxygen by nasal catheter, obtaining slight relief, and part of the time she spent in an oxygen tent, with moderate relief. On June 21, she was returned to the oxygen chamber, the oxygen concentration being 45 per cent. On the following day the dyspnea and orthopnea were greatly decreased. The patient was kept in this atmosphere for seventeen days, at the end of which time her condition was improved, there was no orthopnea, little epigastric distress and a slight cough. The edema of the legs and the ascites had decreased considerably, but had not disappeared entirely. The oxygen concentration in the chamber was then lowered to 19 per cent for five days. Dyspnea and orthopnea reappeared and the patient's vital capacity was only 520 cc. The liver was palpable almost to the umbilicus. There was a reaccumulation of edema, and decrease of the urinary output. In the next three days with the oxygen concentration at 25 per cent, she showed definite improvement, and the urinary output increased. The concentration of oxygen was then raised to 42 per cent, and the patient experienced a return of general comfort and increased diuresis. During the three days before she was returned to the ward, the oxygen concentration was gradually lowered, and she was removed from the chamber with no increase in dyspnea or orthopnea. In the ward she continued to improve, her vital capacity increasing to 940 cc. The urinary output was strikingly increased over the intake of fluids during the patient's residence in an atmosphere containing a high degree of oxygen and lowered during the periods when she inhaled a low amount of oxygen. She was finally able to sit in a chair, and on August 1 she left the hospital much improved. Later, while at home, decompensation again developed, dyspnea and edema increased progressively, and she died on October 29.

CASE 2—History—J. McQ., a white man, aged 53, was admitted to the hospital on Aug. 13, 1929, with diagnosis of cardiac insufficiency and hypertrophy, aneurysm of the ascending aorta, chronic cardiac valvular disease, aortic and mitral insufficiency, chronic myocarditis, general arteriosclerosis and hydrothorax on the left side. For the preceding three years he had suffered from attacks of epigastric pain, radiating to the sternum and interscapular region, accompanied by increasing dyspnea, orthopnea and swelling of the extremities. During the six weeks before the patient's admission the symptoms had become worse and the

patient entered the hospital for the third time. There was no history of rheumatic or syphilitic disease. The Wassermann reaction of the blood was repeatedly negative. The blood urea was 0.38 Gm per liter.

Physical Examination—The patient was tall, gaunt and middle-aged, dyspneic, slightly cyanotic and markedly prostrated. The heart was enormously enlarged, and the left border could be felt in the anterior axillary line. There was marked systolic expansion of the wall of the chest on both the left and the right side. There was a continuous double murmur in the aortic area, transmitted into the neck and audible at the apex. The blood pressure was 130 systolic and 30 diastolic. On the previous admission fluoroscopy had showed marked extensive pulsation of the right margin of the heart shadow and intrapericardial aneurysm. The liver was palpable below the costal margin. There were pitting edema in the lower half of both legs and signs of fluid in the lower half of the left side of the chest. The basal metabolic rate was +29 per cent. Two days after admission, the patient's vital capacity was 1,510 cc.

Course—After three days in the ward, during which the patient failed to improve and continued to be critically ill, he was transferred to an oxygen chamber with a concentration of oxygen of 45 per cent. On the following day, dyspnea was relieved, cyanosis was absent, and he was much more comfortable. The vital capacity at this time measured 2,050 cc. Two days after he had entered the oxygen chamber the urinary output rose from 500 to 1,700 cc. The temperature, pulse rate and respiratory rate gradually decreased. General improvement continued during the following eighteen days' residence in the oxygen room, the vital capacity rose to 2,600 cc, and the edema of the legs diminished.

The oxygen concentration in the chamber was then lowered gradually in forty-eight hours to 20 per cent and was maintained at that level for four days. The patient's condition became progressively worse, with increased dyspnea, cyanosis, rapid pulse and respiration and rise in temperature, accompanied by a fall in urinary excretion and a drop in vital capacity to 1,490 cc. The oxygen concentration was again raised to 45 per cent with a gradual return, within the next week, of the patient's previous comfortable condition. During the following ten days diuresis continued, until he was completely free from edema of the extremities and from fluid in the chest. The oxygen concentration was again gradually lowered to 21 per cent in forty-eight hours, and the patient was removed to the ward. There was a temporary slight return of dyspnea and general discomfort, with elevated pulse and respiratory rates and a fever which continued for three days. During the next month he remained in the ward in fairly good condition without oxygen, but he had occasional attacks of dyspnea. At the end of this time the vital capacity was 1,510 cc. Later he failed gradually, he became increasingly dyspneic and cyanotic, had severe substernal pain, and required large amounts of morphine. He died on December 14.

CASE 3—History—J. Sn., a white man, aged 30, was admitted to the hospital on Dec. 20, 1929, with the diagnosis of interstitial pneumonia, cardiac hypertrophy and insufficiency, adherent pericardium, ascites, generalized edema, atrophic rhinitis, chronic pharyngitis and intestinal hemorrhage. Seven years before admission the patient had been troubled with nasal exudate, dryness of the throat and cough. For five years there had been progressive dyspnea on exertion, fatigue, cyanosis, productive cough and clubbing of the fingers. He had been confined to his bed for much of the time during the past year, and for a month there had been increasing generalized edema. He had been at Bellevue Hospital, but at the suggestion of Dr. James A. Miller had been transferred to the Presbyterian Hospital for further treatment.

Physical Examination—The patient was dyspneic and orthopneic, with a puffy face, generalized edema and marked grayish cyanosis of the skin and mucous membranes. The fingers were clubbed, and the nail-beds were markedly cyanosed. The nasal mucous membranes were atrophic and there was much crusting, the pharynx was congested. There was marked dullness over the upper lobes of both lungs, with harsh bronchial breathing and many moist râles. The heart was enlarged to the left and right, the rate was rapid with a gallop rhythm during inspiration, and the pulmonic second sound was accentuated. The liver was enlarged, and the edge of the spleen was palpable. There was moderate generalized peripheral edema and ascites.

Examination of the blood showed red cells, 6,500,000, and hemoglobin, 108 per cent (Sahli), the Wassermann reaction was negative. The blood urea was 0.35 Gm per liter. Examination of the sputum was negative for tuberculosis. A roentgenogram of the chest showed a dense infiltrative process spreading upward and laterally from the hilus on both sides. Fluoroscopy of the heart showed general enlargement, a dilated conus and slight fixation of the pericardium with change of position.

Course—During the patient's first week in the ward, he became definitely worse, cyanosis, edema and respiratory discomfort increased. His temperature varied between 101 and 102 F. On December 28, he was transferred to an oxygen chamber containing 45 per cent of oxygen, subjective improvement and decrease of cyanosis were noted within a few hours. The urinary output was more than doubled on the second day after transfer from the ward, and this increase was maintained (on the average) for the next two weeks. On his fifth day in the oxygen chamber an intestinal hemorrhage suddenly developed, and in the next thirty-six hours the patient lost about 1.5 liters of blood. He was drowsy, seemed weak and had a marked tachycardia. His fever, which since admission had continued its gradual rise, dropped to normal by crisis at the end of the second day of hemorrhage (Jan 2, 1930). The bleeding thereafter gradually stopped, its cause was not found. On January 7, he was again transferred to the ward, and oxygen was administered by nasal catheter at about 4 liters per minute. Diuresis continued, and by January 14 all edema had disappeared. The signs in the lungs seemed to clear slightly. A moderate cyanosis persisted. This regimen was continued for the next two months. Other medication—potassium iodide in large doses and ethyl iodide by inhalation—was tried, with no apparent effect. On March 14, the administration of oxygen was discontinued, for the next two weeks his cough and cyanosis grew worse, and the temperature rose and the pulse rate increased steadily. The urinary output was decreased, and the weight increased, though there were no definite signs of peripheral edema. The administration of oxygen by nasal catheter again produced increased urinary output and the loss of 9 pounds (4.1 Kg) in weight. This treatment was continued for two months longer, when the patient was transferred to the Montefiore Hospital for a month, during which time no oxygen was administered. He was then (July, 1930) ambulatory and well enough to go home. At present, May, 1931, he is at home ambulatory, but not able to work.

CASE 4—History—M. G., a white woman, aged 52, was admitted to the hospital on June 22, 1929, with the diagnosis of cardiac insufficiency and hypertrophy, auricular fibrillation, chronic cardiac valvular disease, mitral stenosis and insufficiency, aortic insufficiency, hydrothorax and ascites. For the past ten years the patient had suffered from breathlessness on exertion. One year before admission, she had been treated in the hospital for her first attack of cardiac

decompensation For seventeen days prior to the present admission she had complained of severe dyspnea, orthopnea, palpitation and swelling of the extremities

Physical Examination—On examination, the patient was moderately dyspneic, slightly cyanotic, anxious and distressed The heart was markedly enlarged to the right and to the left, the action was irregular, the rate at the apex was 84, the radial rate was 78, a systolic murmur was heard at the apex and a diastolic murmur at the left border of the sternum The blood pressure was 232 systolic and 104 diastolic The lungs showed signs of fluid in the right side of the chest The liver was palpable 7 cm below the costal margin There was moderate edema of the thighs and the ankles The temperature ranged between 100 and 102 F The Wassermann reaction of the blood was negative There was a 40 per cent excretion of phthalein in two hours and a quarter The blood urea was 0.32 Gm per liter

Course—During fourteen weeks' rest in bed in the hospital the patient made no improvement She was transferred to the oxygen chamber with the oxygen concentration at 45 per cent, where she remained for fifteen days, with increased comfort and diminished dyspnea, but without disappearance of the edema At the end of this time, the oxygen concentration was lowered to 30 per cent for twenty-four hours, and the patient was removed from the chamber During the following twenty-four hours she experienced increased dyspnea, lessened comfort and elevation of the pulse rate During the next three weeks her condition grew slowly worse, requiring three thoracenteses She then remained in about the same condition until discharged as a bed case, on December 2 She was last heard from in June, 1930, when she was "doing as well as could be expected"

This patient appeared to have had an active rheumatic myocarditis, accompanied by constant fever She was more comfortable in the oxygen chamber, with lessened dyspnea and orthopnea When she was in an atmosphere containing a high degree of oxygen, although there was no noteworthy diminution in the edema of the legs, she did not require thoracentesis, whereas after she left the chamber thoracentesis was required at almost weekly intervals

CASE 5—History—I B, a white woman, aged 32, was admitted to the hospital on Sept 21, 1929, with the diagnosis of cardiac insufficiency and hypertrophy, chronic cardiac valvular disease, mitral stenosis and insufficiency, auricular fibrillation and acute rheumatic fever Following an attack of pneumonia twelve years before, the patient began to experience shortness of breath after exertion Two years later, she had rheumatic fever with swollen joints For the five years before admission there had been symptoms of progressive decompensation For five weeks she had suffered from increasing dyspnea, pain in the chest and swelling of both legs

Physical Examination—The patient had deep red cheeks, and marked cyanosis of the lips and nail-beds, she was in great distress, being very dyspneic and prostrated The heart was enormously enlarged, the left border could be felt in the anterior axillary line The rate at the apex was 140, that at the wrist, 80 The first sound at the apex was replaced by a loud, metallic, systolic blowing murmur, followed by a soft diastolic murmur The blood pressure was 150 systolic and 80 diastolic Examination of the abdomen showed a large, tender, pulsating liver palpable at the umbilicus Numerous crackling râles were heard

over both sides of the chest posteriorly. There was marked edema of the sacrum and the legs. Examination of the blood revealed red blood cells, 6,740,000, and hemoglobin, 145 per cent. The temperature ranged between 100 and 102 F. A culture of the blood was sterile.

Course—On September 26, after five days of routine treatment in the ward had produced no improvement, the patient was put in an oxygen chamber, in which the concentration of oxygen was 21 per cent, after eighteen hours there was no relief. Oxygen concentration was then increased to 45 per cent and was maintained at that level for seventeen days. After the increase in atmospheric oxygen, the patient was subjectively very much improved. Her breathing became quiet, with little dyspnea, and the cyanosis was much diminished. No effect was noticed on the urinary output, the size of the liver or the edema of the extremities. In three days the hemoglobin decreased to 125 per cent, and the red blood cells to 5,560,000, in six days the former was 110 per cent and the latter, 5,460,000. At the end of seventeen days, the oxygen concentration was lowered to 21 per cent in six hours, and the patient was removed to the ward. She became worse almost at once, with profound cyanosis, sweating and dyspnea. She grew progressively weaker and more prostrated. The pulse rate was very faint. The systolic pressure was 90, and the diastolic could not be counted. She voided no urine, and none was obtained from the bladder on catheterization. She was apparently in a state of shock. Twenty-four hours after she had been moved to the ward, she was returned to the oxygen chamber, improvement was noticed almost at once, with increased strength, easier respiration and better color. After four hours her blood pressure was 120 systolic and 73 diastolic. She voided 125 cc of urine at about the same time. On the following day, she voided 1,000 cc of urine. At the end of three days, her condition approximated that present before her removal from the oxygen chamber. On October 26, after seven more days in the oxygen chamber, the percentage of oxygen was gradually reduced, and on October 29, she was returned to the ward. She held her own fairly well for a while, receiving oxygen by nasal catheter, but then failed rapidly, and died on November 24.

CASE 6—History—J. Sr., a white man, aged 54, was admitted to the hospital on May 25, 1929, with the diagnosis of cardiac insufficiency, chronic cardiac valvular disease, mitral stenosis and insufficiency and auricular fibrillation. For the four years before admission the patient had complained of gradual increase of breathlessness on exertion, with swelling of the abdomen and slight edema of the ankles. He had been in another hospital eight months previously with decompensation, and had been discharged after an eight months' stay. The present attack of dyspnea and the appearance of some edema had begun three weeks before admission.

Physical Examination—The patient was slightly dyspneic and moderately cyanotic, but he had no orthopnea, even when he was lying flat in bed. The heart was enlarged 13.5 cm. to the left in the sixth space, and was slowly fibrillating, with a low systolic and soft diastolic murmur at the apex. The blood pressure was 118 systolic and 94 diastolic. The liver was palpable at the umbilicus. There was slight edema of the extremities. The basal metabolic rate ranged from +2 to +9 per cent, and the vital capacity was 3,300 cc. The Wassermann reaction of the blood was negative. The blood urea was 0.22 Gm. per liter.

Course—The patient was kept at rest in bed in the hospital for three months. The edema disappeared during the first week, and he improved slowly and was up an hour a day in a chair. He was transferred to the oxygen chamber on July 31, in the hope that further improvement in his cardiac reserve could be

obtained During the first week in the chamber, with the oxygen concentration of the atmosphere at 21 per cent, there was no significant change The vital capacity dropped gradually to 2,790 cc The oxygen concentration was then increased to 45 per cent without any improvement in the patient's condition The vital capacity was 2,620 cc While the patient was in the chamber, a cold with a cough developed, and he felt worse for several days Respiration became wheezing, and the lungs were filled with sibilant râles After eight days in the chamber with the oxygen concentration at 45 per cent, the patient was returned to the ward Two days later his vital capacity was 2,720 cc He remained in the hospital for three months after removal from the oxygen chamber, without change in his condition When treatment with oxygen was begun the patient had no edema He had moderate cyanosis, venous in origin, which was not greatly diminished in the oxygen chamber

Thereafter, the disease ran a long course while the patient was in the hospital, and there were several pulmonary infarcts He was finally discharged as a bed case on November 9 He died at home on Feb 13, 1930

CASE 7—History—A S, a white girl, aged 13, was admitted to the hospital on March 7, 1930, with the diagnosis of cardiac insufficiency and hypertrophy, congenital pulmonary stenosis, defect of the intraventricular septum, transposition of the great arterial trunks, hypertrophy of the right ventricle, patent ductus arteriosus and abscess of the brain with rupture into the right lateral ventricle Since the age of 3 years, the patient had been markedly cyanosed, and had suffered increasingly from dyspnea on exertion She had had recurrent attacks of pains in the joints Her fingers had been clubbed for at least five years

Physical Examination—Examination revealed a small, thin girl, lying quietly in bed, hyperpneic but not dyspneic There was extreme cyanosis of the skin and mucous membranes, the lips and tongue were almost black There was clubbing of the fingers and toes The heart was moderately enlarged, with a systolic shock at the apex, a thrill over the third and fourth left interspaces, and double murmurs at the apex and base The second pulmonic sound was sharply accentuated The liver and spleen were not felt There was no peripheral edema Examination of the blood showed red cells, 10,900,000, and hemoglobin, 160 per cent The Wassermann reaction of the blood was negative

Course—The patient was able to walk about the wards without discomfort After three weeks, she was transferred to the oxygen chamber in which the atmosphere contained 45 per cent oxygen, and was there for four days No significant change in her clinical condition was noted She was discharged from the hospital on April 6 On May 7 she was readmitted, with a progressive paralysis of the left side, and she died on May 12 The postmortem observations are indicated in the foregoing diagnosis

CASE 8—History—I S a white man, aged 29, a salesman, was admitted to the hospital on April 28, 1930, with the diagnosis of far advanced chronic pulmonary tuberculosis, the upper lobe of the right lung showed an excavation Right phrenicectomy had been performed The patient had complained of cough for two years and he had had three pulmonary hemorrhages during the year before admission Nine months before, dyspnea on exertion developed, the patient lost weight and more sputum was raised He entered Bellevue Hospital on Jan 1, 1930, and was under treatment there for five months He was found to have advanced tuberculosis, with a large cavity in the right lung During the next two months, artificial pneumothorax was performed by successive injections of air but this was discontinued following renewed hemoptysis On March 11 right

phrenicectomy was performed, two weeks later, a roentgenogram of the lung showed that the cavity had diminished one-half and the patient's general condition was slightly improved. He was transferred to the Presbyterian Hospital for treatment in the oxygen chamber.

Physical Examination—The patient appeared chronically ill, poorly nourished, cyanotic, dyspneic and orthopneic, and he was suffering from violent spasms of slightly productive cough. There was moderate cyanosis of the lips and mucous membranes. On the left side of the chest there were harsh breath sounds over the midlung, with many moist râles, on the right, flatness at the base of the lung (relaxed diaphragm), scattered moist râles with dulness over the upper lobe and an area of amphoric breathing anteriorly. The heart was not enlarged, the sounds were rapid and loud. The patient weighed 100 pounds (45.4 Kg). Examination of the blood revealed red cells, 6,340,000, and hemoglobin, 121 per cent (Sahli). The blood urea was 0.21 Gm per liter. Urinalysis gave negative results. On several occasions, examination of the sputum was positive for tuberculosis. A roentgenogram showed dense infiltration over the upper lobe of the right lung, with a cavity at the apex, and fresh infiltration in the left lung.

Course—The patient was in the oxygen chamber throughout his stay of eleven weeks in the hospital. During the first week the oxygen in the atmosphere was kept at 21 per cent. The patient was greatly exhausted by a racking cough. His appetite was poor, and he vomited frequently. The oxygen was then raised to from 45 to 50 per cent and was maintained at that level. The cyanosis cleared up almost at once and did not recur. During the succeeding weeks, clinically, there seemed to be a slow but definite improvement. There were less cough and less dyspnea, the patient was not orthopneic, and he gained 4 pounds (1.8 Kg). The red blood cells decreased from 6,340,000 to 5,400,000, and the hemoglobin from 121 to 95 per cent. The vital capacity decreased from 1,500 cc to 1,000 cc. There were fewer râles in the lungs. A roentgenogram showed that there were no marked changes in the lungs. During the week of May 26 to June 1, the patient had several small hemoptyses. Throughout his stay in the hospital his temperature remained between 99 and 100 F. During the last five days (from July 10 to 14) the oxygen was gradually reduced in the chamber to atmospheric level, and the temperature raised, there were no untoward symptoms, and on July 15, he was again transferred to the Bellevue Hospital.

Book Reviews

RHEUMAPROBLEME GESAMMELTE VORTRÄGE GEHALTEN AUS DEM II. ARTZEKURSUS DES RHEUMA-FORSCHUNGS INSTITUTS AM LANDESBAD DER RHEIN-PROVINZ IM AACHEN Volume 2 Price, 12 marks Pp 176 Leipzig Georg Thieme, 1931

This volume contains lectures on chronic rheumatism given to physicians

The pathogenesis and clinical manifestations of chronic diseases of the joints are discussed by Prof. Herbert Assman of Leipzig. He considers the two types of chronic arthritis—infectious and osteoarthritis—and logically advises that as osteoarthritis is not infective, the better term is osteoarthrosis.

Prof. Richard Burling of Frankfurt discusses experimental infective arthritis. He supports the generally accepted view that chronic infective arthritis, as found in man, has not been reproduced experimentally. He relates in detail the changes in the joints observed in horses used for the preparation of diphtheria antitoxin.

Roentgenograms of acute and subacute joint inflammation are presented by Prof. Gottfried Boehm of Munich. The inflammation of joints associated with acute infection is discussed in detail.

Prof. Christian Bruhn of Dusseldorf presents a complete chapter on the importance of stomatological studies and their possible relation to chronic rheumatism.

The differential diagnosis of rheumatism from certain other diseases in children is discussed by Prof. Albert Eekstein of Dusseldorf. This chapter is well illustrated by roentgenograms.

Prof. Anton Fischer of Aix-la-Chapelle stresses the importance of medical experts in national health insurance in order to secure a proper diagnosis and prognosis in the various disturbances of the joints.

The chapter on the influence of therapeutic measures on infectious arthritis by Dr. Heinz Gehlen of Aix-la-Chapelle deals chiefly with the teeth and tonsils as foci of infection and the therapeutic value of their removal.

The doctrine of focal infection in rheumatic diseases given by Prof. Siegfried Graff (Hamburg) is presented, as the author states, from a theoretical standpoint. He discusses the etiology of rheumatism, or at least the symptom complex that is referred to as rheumatism.

So-called rheumatism of the spine is presented by Dr. Walter Krebs of Aix-la-Chapelle. Following the present conception, he considers two types: spondylarthritis ankylopoietica, synonymous with the "poker spine" in the American literature, and spondylitis deformans, synonymous with osteoarthritis. The former he attributes to an infection, the latter, to acute trauma or overuse.

There is a brief chapter on the heart and chronic rheumatism by Prof. Franz Kulbs (Cologne).

Dr. Stephan Loewe (Breslau), consultant to a dental institute for the treatment of patients carrying social insurance, which includes dental care, is optimistic over the value of removing dental infection in chronic rheumatism.

The present state of knowledge regarding the etiology of infectious rheumatism is reviewed by Prof. Paul Manteufel (Dusseldorf). He gives a complete review of the literature, stating that in Germany the question of a specific rheumatic virus is treated in a "stepmotherly manner." He questions the probability of a specific micro-organism. This chapter is excellent.

Prof. Walther Müller (Königsberg) discusses the biologic basis of disturbances of the joints.

Nutrition and nutritional disturbance and their relation to so-called rheumatism are presented by Prof. Hermann Strauss (Berlin). He takes up calcium, phosphorus, nitrogen and sugar metabolism and the relation of obesity to osteoarthritis. He also discusses the basis of various dietary procedures.

The endocrine glands and diseases of the joints are discussed in detail by Prof S J Thannhauser (Freiberg). He also reviews the literature on the rôle of the endocrines in Perthes', Kohler's and Kienbock's diseases. This chapter is profusely illustrated.

These discussions have been prepared with great care. The literature is thoroughly reviewed, and, in addition, personal experience is recorded. The references in the bibliography will be of great assistance to those who wish to study the sources of information. This volume is a valuable addition to the literature on chronic diseases of the joints.

TEXTBOOK OF SURGERY By JOHN HOMANS Price, \$9 Springfield, Ill
Charles C Thomas, 1931

This is a well bound volume of nearly 1,200 pages, evidently intended as a student's textbook in surgery. There are more than 500 illustrations, mostly of a schematic sort, but which amply demonstrate the points intended. It is a rather ambitious attempt to cover not only the field of general surgery, but all of the surgical specialties as well, including ophthalmology, otolaryngology, gynecology and urology.

The work is assembled in rather an original manner, being compiled from either the lecture notes or the complete written lectures of various members of the department of surgery of Harvard Medical College, and therefore represents the collaboration of an extremely prominent group of specialists. Dr Homans says in the introduction that the material with which he worked was exceedingly varied, some of it consisted of rather sketchy lecture notes which he amplified into the text, while some of it was received with the text nearly as it is printed.

The work is decidedly provocative, and the reviewer cannot help being impressed with the refreshing newness of the manner of presentation as well as with a number of glaring faults. The style is breezy and makes entertaining reading, being practical in the extreme. All unnecessary classifications are left out, and the all too brief descriptions of diseases and their treatment make a lasting impression on the reader's mind because of the often colloquial English in which they are couched. Even the names of conditions are at times withheld (as in carcinoids of the appendix), although a number of lines are devoted to a description of the condition.

The routine treatment of many surgical diseases has been handed down from one textbook to another, even compiled for generations, and in that sense this work represents a decided advance, because it is based on the extraction of real medicine from the material presented to students and probably not so much on the diseases and complications from other textbooks. For that reason the more common conditions receive their share of emphasis, often at the expense of certain rarer diseases and complications. One cannot help feeling that a student who has studied this work carefully would probably not stand high in a competitive examination, but would make an eminently practical physician.

Many of the statements made in the book would seem, in the opinion of some surgeons at least to be categorically wrong. This is especially true of the choice of treatment, as in the majority of cases the author attempted to tell the student only the best treatment, and such matters are often open to discussion. An example is the entire omission of Sayre's dressing as a treatment for a fractured clavicle, or the statement that the worsted truss will cure infantile hernia, whereas in the opinion of most students of hernia, it is worthless, also, the statement that most retroperitoneal tumors are inoperable is untrue. Such criticisms could be multiplied almost indefinitely, but the reviewer feels that this should not prevent a wide adoption of the book as a surgical textbook on account of its many advantages.

One of the interesting features of the book is the author's contribution to medical history. Nearly every appliance, disease or treatment for disease is traced back to its original source, and, as a consequence, the amount of historical

material presented is truly astounding. In many cases, also, this is offered in such a way that it has a direct bearing on the treatment and diagnosis and therefore does not represent something more for the student to learn.

CLINICAL DIAGNOSIS BY LABORATORY METHODS By JAMES CAMPBELL TODD, PH B, M D, Late Professor of Clinical Pathology, University of Colorado School of Medicine, and ARTHUR HAWLEY SANFORD, A M, M D, Professor of Clinical Pathology, University of Minnesota (Mayo Foundation), Head of Section on Clinical Laboratories, Mayo Clinic. Seventh edition, thoroughly revised. Cloth. Price, \$6. Pp 765, with 347 illustrations, 29 in color. Philadelphia: W B Saunders Company, 1931.

This text, now published in the seventh edition with Sanford as co-author, has for many years served a useful purpose in courses of laboratory instruction as a text and in clinical laboratories as a guide. It ranks with other American texts, such as that of Cummer, in the choice and extent of material presented. The eleven chapters, exclusive of the introductory paragraphs on the use of the microscope, cover adequately routine examinations of the sputum, the urine, the blood, the gastric and duodenal contents, the feces, certain animal parasites, exudates and tissue fluids, miscellaneous examinations, serologic methods, bacteriologic technic and vaccines and biologic tests of the skin. A short appendix is devoted to instructions of a general character, including the preparation of solutions. The subject material is well organized and meets adequately the demands of a text for students and of a guide for clinical laboratories.

THROUGH THE ALIMENTARY CANAL WITH GUN AND CAMERA. A FASCINATING TRIP TO THE INTERIOR. Personally conducted by GEORGE S CHAPPELL. Introduction by Robert Benchley. Cloth. Price, \$2. Pp 231, with illustrations. New York: Frederick A Stokes Company, 1930.

Dr. Walter Traprock, author of the famous "Traprock Trilogy," herein presents an amusing, farcical tale of an excursion through the human alimentary tract as far as the colon and return. The return journey is equally humorous, but is decidedly more perilous in every respect. "The Calomels Are Coming" is the theme song. The illustrations are cleverly adapted to the text and add greatly to the enjoyment of the book, which is worth a few hours of anybody's time.

EXOPHTHALMIC GOITER

THE DEVELOPMENT OF REFRACTORINESS TO IODINE¹

WILLARD OWEN THOMPSON, M D

AND

PHEBE K THOMPSON, M D

CHICAGO

Soon after the treatment for exophthalmic goiter with iodine became general, it was recognized that during prolonged administration the basal metabolism often rose markedly after an initial drop, in association with an increase in the severity of the disease. Nevertheless, the impression has prevailed that as long as iodine is being given in excess the peculiar nervous manifestations of exophthalmic goiter are completely under control, regardless of what happens to the rate of the basal metabolism¹. Certain observations that we have made suggest that this may not always be the case.

During the continuous administration of iodine in the following case, the patient, after initially showing a marked response to the administration of about 6 mg (1 drop of the compound solution²)

¹ Submitted for publication, Dec 23, 1930

From the Thyroid Clinic and Metabolism Laboratory, Massachusetts General Hospital, Boston, the Department of Medicine, Rush Medical College and the Presbyterian Hospital, Chicago

1 This appears to be largely the result of a rather general acceptance of Plummer's ingenious hypothesis. Plummer said "Lugol's solution controls only the abnormal product. We have not seen that phase of the exophthalmic goiter picture which we attribute to the abnormal product become more marked while the patient was on Lugol's solution. Theory and experience seem to indicate that the amount of the normal product sometimes increases when the patient is taking iodine" (Plummer, H S, in discussion of Mason, E H. Iodine Therapy in Toxic Goitre, *Tr A Am Physicians* **39** 167, 1924). Elsewhere he said "Is the control of that part of the complex attributed to an abnormal product absolute? In other words, will the administration of Lugol's solution in cases of exophthalmic goiter in amounts somewhere between 10 and 40 minims daily from the inception of the disease ever be followed by the characteristic complex even though hyperthyroidism becomes intense? That the evidence warrants seriously considering an affirmative answer is significant" (Mayo, C H, and Plummer, H S. *The Thyroid Gland*, St. Louis, C V Mosby Company, 1926, part 2, p 77).

2 We have previously shown that this is roughly the minimum dose of iodine that will produce a maximum reduction in the rate of basal metabolism in most cases of exophthalmic goiter that occur in Boston (Thompson, W O, Brailey, A G, and Thompson, P K. *The Effective Range of Iodine Dosage in Exophthalmic Goiter*. Preliminary Report, *J A M A* **91** 1719 (Dec 1) 1928. Thompson, W O, Brailey A G, Thompson, P K., and Thorp, E G. *The Range of Effective Iodine Dosage in Exophthalmic Goiter*. I. The Effect on Basal Metabolism of Rest and of the Daily Administration of One Drop of Compound Solution of Iodine. *Arch Int Med* **45** 261 [Feb] 1930).

daily, slowly became completely refractory to this dose, both from the standpoint of basal metabolism and from that of signs and symptoms. Exophthalmos first appeared as refractoriness developed.

REPORT OF CASES

CASE 1—The patient, Miss A P Y³ (chart 1), an unmarried Nova Scotian girl, aged 21, entered the Massachusetts General Hospital, on June 15, 1927, with a slightly atypical case of exophthalmic goiter. There were no ocular signs, and the intelligence was perhaps slightly below the average. In spite of this, however, the patient was unusually cooperative. It was decided by the medical service concerned to determine the accuracy of the diagnosis by various manipulations of iodine therapy before proceeding with surgical intervention. The only basal metabolism test performed before the beginning of iodine therapy was done in the outpatient department on June 7, and gave a result of +69 per cent. During rest in bed and the administration of compound solution of iodine, the metabolic rate dropped to +11 per cent. The patient was discharged and iodine was omitted. Within eight days the rate of metabolism had risen to +73 per cent and most of the characteristic signs and symptoms of exophthalmic goiter were present, except exophthalmos. Compound solution of iodine was again given in a dose of 1 drop daily, and within eight days the metabolism dropped to +27 per cent, and there was a striking clinical improvement. Shortly afterward the dose was increased to 15 drops daily, and finally to 30 drops daily. It seems that on the administration of 30 drops the rate of metabolism dropped temporarily to a lower level than on the administration of 1 drop daily, although it quickly rose again to the former level. After a total period of twenty-three days, the large doses were discontinued, and a dose of 1 drop was again employed daily. On the administration of this dose the rate of metabolism slowly rose, and a gradual increase in the severity of the clinical signs and symptoms was associated with this rise. Sixty-two days after this dose was started again, the rate was about +55 per cent. At this point the dose was increased to 30 drops daily. Within six days the rate dropped to about +35 per cent, and at the same time a slight clinical improvement associated with a gain in weight took place. At the end of ten days the dose was increased to 90 drops daily and, during a period of one week, this did not produce significant further reduction in the metabolic rate or further clinical improvement. A dose of 1 drop daily was then resumed, and the metabolism rose from a level of +33 per cent on November 4 to a level of +80 per cent on December 1. As the metabolic rate was thus rising, all of the signs and symptoms of the disease, including the emotional instability, slowly became more intense, and by December 1 the disease was more severe than it had been previously. Nervousness and irritability were marked. The patient perspired profusely. There was pronounced flushing of the skin, and the patient wept on slight provocation. Two months before this, the

3 Part of the data in cases 1 and 2 have been recorded elsewhere to illustrate other points (Thompson, Brailey, Thompson and Thorp [footnote 2, second reference] Thompson, W O, Thompson, P K, Brailey, A G, and Cohen, A C. Prolonged Treatment of Exophthalmic Goiter by Iodine Alone, *Arch Int Med* 45 481 [April] 1930).

eyes first began to be somewhat prominent Iodine was omitted on December 1, and no significant change was noted either in the disease itself or in the metabolism until Jan 24, 1928, when a spontaneous reduction had occurred associated with a slight decrease in the severity of the disease. On February 3, the administration of compound solution of iodine was started again in a dose of 1 drop daily. By February 9 the rate of basal metabolism had dropped from +65 per cent to a level of about +35 per cent. There was no further reduction in the metabolic rate when the dose was increased to 10 drops daily. Shortly afterward the patient was admitted to the hospital, where, in association with rest in bed, the rate of metabolism dropped to a level of about +20 per cent. A subtotal thyroidectomy was performed on February 28 and was followed by an uneventful convalescence.

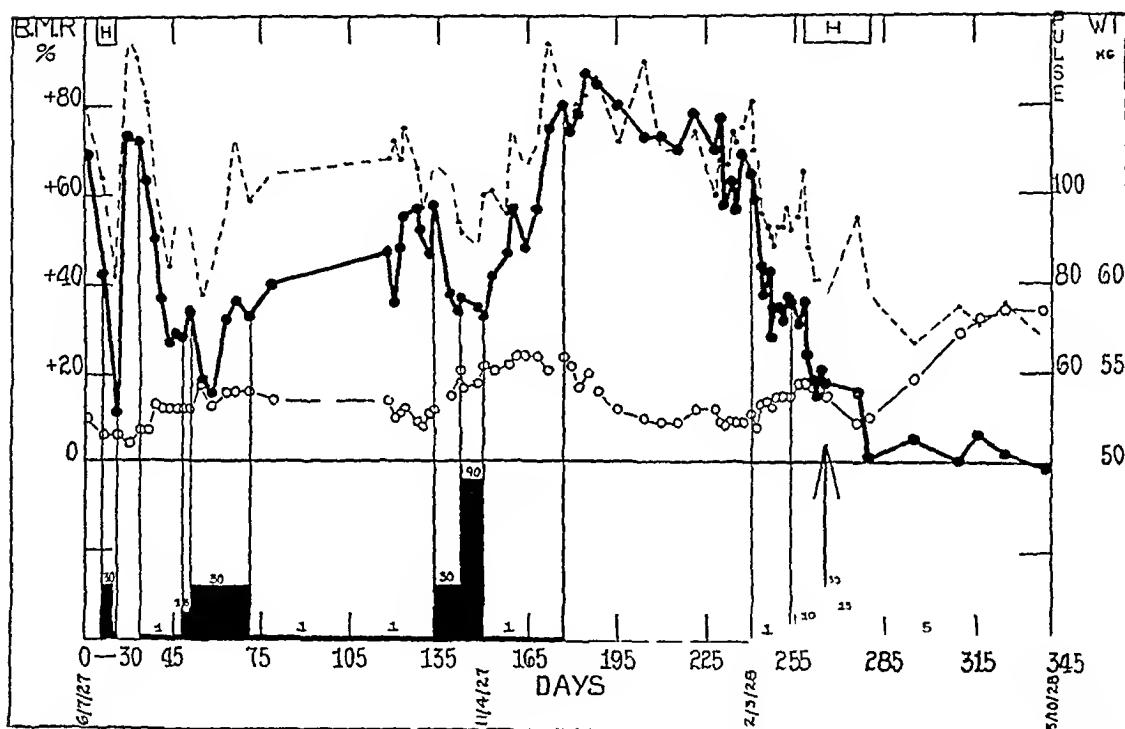


Chart 1 (case 1)—The development of complete refractoriness to 1 drop of compound solution of iodine daily during its prolonged administration to a patient with exophthalmic goiter. Its development was preceded by a well marked response to this dose and was followed by a well marked response to it after a period of omission of iodine. The initial short period of iodination did not appear to be associated with the development of refractoriness, whereas the prolonged administration was. In this and subsequent charts, black areas denote periods of treatment with compound solution of iodine, and the figures above them, the daily doses in drops, arrows, subtotal thyroidectomies, half arrows, hemithyroidectomies, *H*, a period of hospitalization. The black line indicates the basal metabolic rate, the circle line, the weight in kilograms, and the dash line, the pulse rate.

The following case is similar to the first in that, during the continuous administration of iodine, the patient showed an initial improvement, and then a gradual increase in the intensity of all of the signs

and symptoms, including the peculiar nervous manifestations. The eyes first began to increase in size as the basal metabolic rate rose during the administration of iodine. Unlike the first case, however, the condition became only partially instead of completely refractory to small doses (about 6 mg of iodine administered daily)

CASE 2—The patient, Mrs E H. (chart 2), a married woman, aged 26, first came to the metabolism laboratory of the Massachusetts General Hospital on Oct 10, 1927, complaining chiefly of dyspnea. The rate of basal metabolism at that time was +22 per cent. The catamenia had begun to be scanty, she had diarrhea and had lost 33 pounds (15 Kg). There were no ocular signs. The thyroid gland was firm and symmetrically and moderately enlarged with a soft

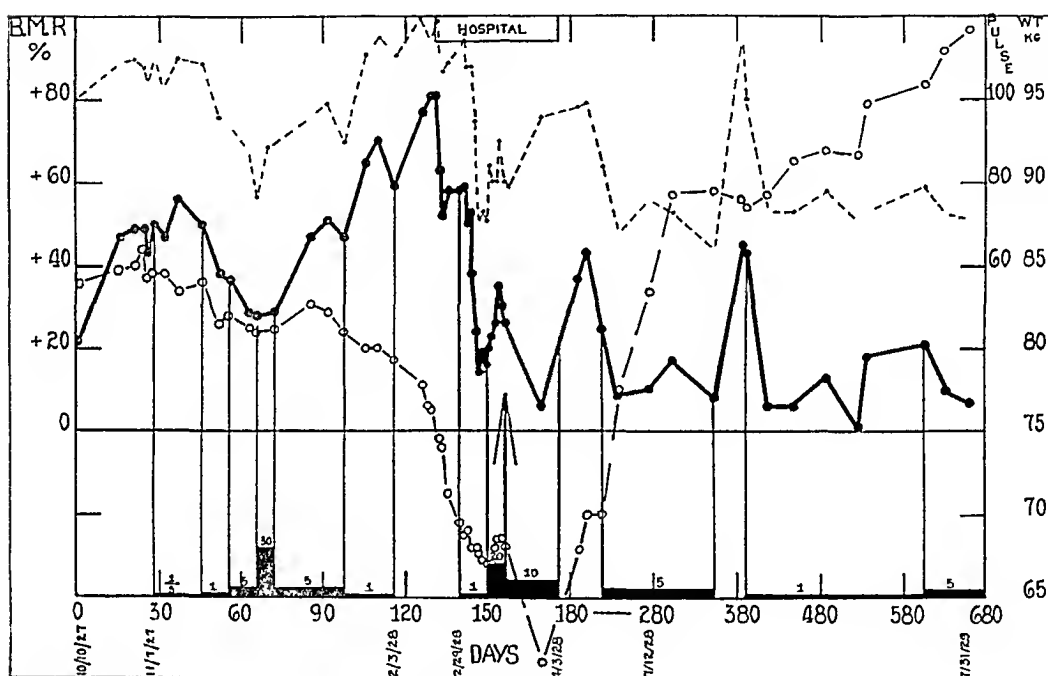


Chart 2 (case 2)—The development of partial refractoriness to 1 drop of compound solution of iodine daily during prolonged administration, and recovery from this refractoriness on the omission of iodine

systolic bruit all over, most marked at the superior poles. There was a fine tremor, and the skin was warm and moist. The onset of the disease had apparently occurred eleven months previously, and the goiter had been noticed six months before the patient came to the hospital. It was decided to give iodine as a therapeutic test. While a metabolic level was being secured, the rate of basal metabolism rose to about +50 per cent. It remained at this level from October 26 until November 7, when the administration of compound solution of iodine was started in a dose of 1 drop of a 20 per cent solution daily. This produced no change, except, perhaps, to make the thyroid gland slightly larger and firmer. On November 25, the dose was increased to 1 drop of the undiluted solution daily. While this dose was being administered, the rate of metabolism dropped to +37 per cent, and the patient felt less nervous and tired less easily. On December 5, the dose of iodine was increased to 5 drops daily. On the administration of this

dose the improvement was more marked, and the rate of metabolism dropped to $+28$ per cent. On December 15, the dose was increased to 30 drops daily. This did not produce a further reduction in the rate of basal metabolism or further clinical improvement. The thyroid was much firmer and somewhat larger during the administration of 30 drops daily than before the iodine therapy was begun, and the bruit had become less marked. On December 22, the dose of iodine was reduced to 5 drops daily. On this dose the rate of basal metabolism rose to a level of $+48$ per cent. The patient was more irritable, had more palpitation and complained of frontal headaches. There was no reduction in the size or firmness of the thyroid, over which there was a faint bruit. The latter was much less marked than before the use of iodine, although the rate of metabolism was the same. On Jan 16, 1928, the dose of compound solution of iodine was reduced to 1 drop daily. On this dose the rate of metabolism promptly rose to about $+65$ per cent, and the patient was more nervous, slept more poorly, had more frequent crying spells and more palpitation, fatigued more easily and perspired more profusely. She had a marked tremor. The thyroid continued to be very firm, but seemed slightly softer than it had been during the administration of 30 and 5 drops daily. There was a faint bruit at the right superior pole. For the first time, the eyes began to smart and water and to cause pain when she read. They appeared somewhat full, but there was no definite lid lag. At about this time the family began to notice that the eyes were more prominent than they had been. On February 3 iodine was omitted, and the patient became still worse. She had still more palpitation and dyspnea on the slightest exertion, and the diarrhea returned. The thyroid continued to be firm for some time. She was admitted to the hospital on February 17. On February 18, it was noted that the right eye was larger than the left, and that there was a bilateral lid lag. The patient was more ill than at any time since she had been under observation. She thrashed about in bed. She was emotionally unstable, extremely short of breath and perspired profusely. She appeared washed out. The goiter was even harder and firmer than before the administration of iodine was begun. However, by February 23, it was noted that the thyroid was much softer than on admission. By February 25 she had vomited several times. The marked toxicity during this period was reflected in the rapid loss of weight. With only rest in bed, the rate of metabolism dropped from $+81$ to $+58$ per cent. On February 29, the administration of compound solution of iodine was started in a dose of 1 drop daily. By March 6 the rate of the metabolism had dropped to about $+16$ per cent. The vomiting had stopped, the patient was much quieter, and the thyroid had again become firmer, although a soft systolic bruit persisted, which was more marked on the right than on the left. On March 8, the dose was increased to 30 drops daily, but this produced no further reduction in the rate of basal metabolism, in fact the rate rose slightly on this dose. A subtotal thyroidectomy was performed on March 15, 1928. The immediate convalescence was somewhat delayed by a pulmonary infection, but otherwise was uneventful. Although the thyroidectomy was extensive, within about one month afterward, the basal metabolic rate rose to $+37$ per cent, and the thyroid tissue had begun to regenerate. However, up to the time we left Boston it had been possible to hold this persistent thyrotoxicosis in check by the administration of iodine.

The following case is similar to the preceding one in that the condition became partially and not completely refractory to treatment with iodine (5 drops of the compound solution daily). Exophthalmos increased as the rate of metabolism rose during the administration of iodine.

CASE 3—The patient, Mrs E R⁴ (chart 3), a married woman, aged 34, was admitted to the outpatient department of the Massachusetts General Hospital on Dec 27, 1928, with a typical case of exophthalmic goiter. There was well marked exophthalmos, lid lag, tremor and marked emotional and vasomotor instability (particularly for the preceding six months). For three years the thyroid gland had been diffusely enlarged, and there was a bruit over it. During the administration of 1 drop of compound solution of iodine daily the rate of the basal metabolism dropped from a level of +45 per cent on Jan 15, 1929, to +19 per cent on January 22, and a marked clinical improvement was noted. Slight reduction in exophthalmos had occurred by February 12. The thyroid gland, which was soft before the administration of iodine, became hard and firm. The administration of

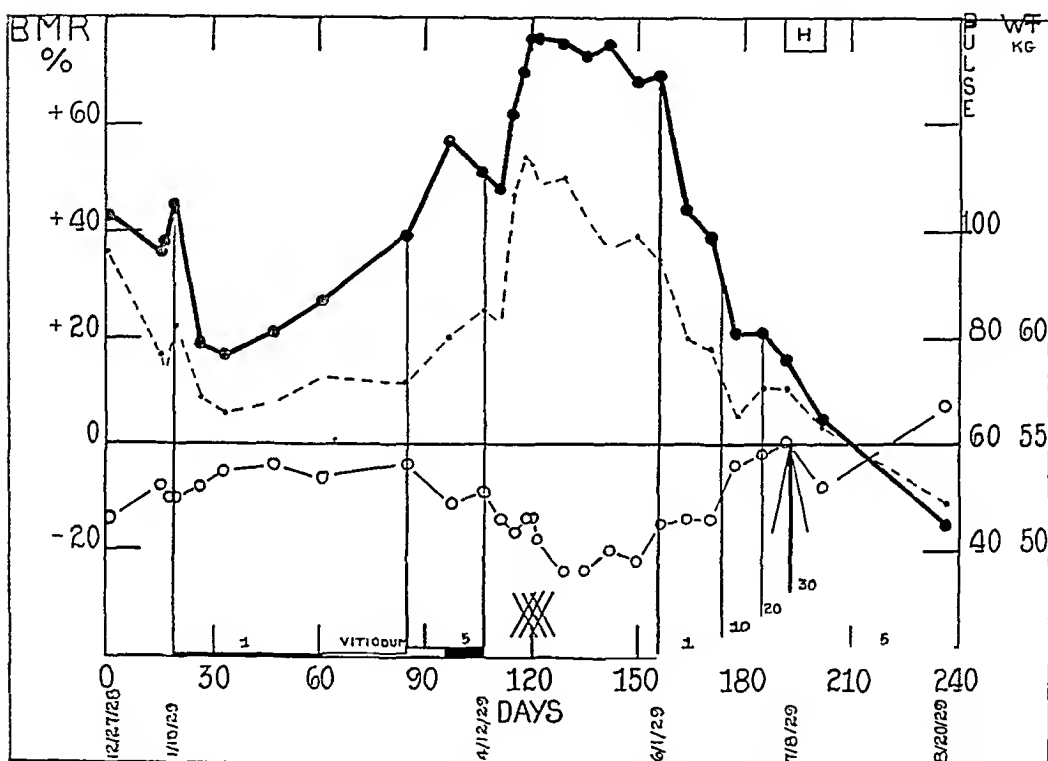


Chart 3 (case 3) —The development of partial refractoriness to 5 drops of compound solution of iodine daily during the prolonged administration of iodine, and recovery from this refractoriness on the omission of iodine. X denotes roentgen treatment

iodine was continued, and by about February 26 the rate of basal metabolism had begun to rise. Increasing the dose of iodine about one month later to 5 drops of the compound solution daily did not appear to prevent a further rise. By March 21, when the basal metabolism was +39 per cent, the patient was more nervous and irritable than she had been, but not as much so as before treatment with iodine was begun. By April 2, 1929, the rate of basal metabolism had risen to +57 per cent and the patient was much worse. She was unable to sit

4 Part of the data on this patient has been recorded elsewhere to illustrate another point (Thompson, Thompson, Brailey and Cohen [footnote 3, second reference])

still, she was more nervous, she perspired more profusely, and she was more emotionally unstable than she had been previously. The right eye had again increased in size. Most of the time she was depressed, frightened and very suspicious. The thyroid gland had become very hard. Having already had experience with such cases, we decided to omit treatment with iodine for a period before proceeding with surgical intervention. This was done on April 12, and the rate of metabolism rose about 20 points during the next thirteen days to a level of about +75 per cent, and the disease became still more severe. The thyroid gland slowly became softer again. The subsequent course of the disease was complicated by the fact that the patient was given three roentgen treatments (at her request), which were followed by a slight clinical improvement but no significant change in the basal metabolic rate. After an interval of fifty days, iodine was readministered, first in a dose of 1 drop of the compound solution daily and then in a dose of 10 drops daily. This produced a reduction in the rate of basal metabolism from +69 per cent to +21 per cent and an improvement in the disease. A subtotal thyroidectomy, performed shortly afterward, was followed by only a slight reaction, and the patient made an uneventful recovery.

The following patient, who had a severe case of exophthalmic goiter, was apparently refractory to iodine (250 mg daily) on admission to the hospital, after taking the compound solution continuously for one month. Owing to a rapid pulse rate at the time of the first appearance in the operating room, the surgeon did only a bilateral ligation of the superior thyroid arteries. A subtotal thyroidectomy was performed about eleven weeks later. Each operation was preceded by a period of omission of iodine therapy. Judging by the uneventful convalescence from each operation and from the course of the basal metabolism, it is probable that a subtotal thyroidectomy could have been done the first time the patient was taken to the operating room, although at the time the alternative decision seemed wise.

CASE 4—The patient, Mrs. A. A. (chart 4), a married woman, aged 23, was admitted to the Woodyatt service of the Presbyterian Hospital on March 17, 1930, complaining of nervousness of three years' duration and of fatigability, profuse perspiration, generalized itching, loss of weight, increased appetite, weakness, increased thirst, polyuria, palpitation, irritability and scantiness of menstruation of three months' duration. The patient was restless and constantly moved about. Loud laughter alternated with profuse weeping. There was a well marked tremor of the extended fingers. There was puffiness of the upper and lower eyelids and a stare, but no lid lag. The thyroid was hard and firm, and there was no bruit over it. At the time of admission, the patient had been given 30 drops of compound solution of iodine daily for about a month, and the metabolic rate was +110 per cent. Feeling that this indicated that the condition was refractory to iodine, this medicine was omitted on the day of admission. In spite of this, the rate of basal metabolism dropped to a level of about +80 per cent, except for a slight temporary rise associated with menstruation (the only menstrual period while the patient was in the hospital). By March 24 the thyroid had become fairly soft, and by March 31 it had become still softer and had decreased to half its previous size. A systolic bruit was present all over, most marked at the superior poles. There was no increase in the emotional instability and no increase in the size of

the cys On March 31 the administration of compound solution of iodine was started in a dose of 10 minims (0.6 cc) three times daily. The rate of basal metabolism dropped to a level of about +55 per cent by April 7. After the administration of iodine the thyroid again began to increase in size. By April 4 it was nearly twice its size on March 31, but it did not become hard until April 10. In association with the drop in metabolism, the signs and symptoms of the disease decreased, but they did not disappear, as shown by the following note of April 11: "All the symptoms of the disease persist in a somewhat subdued form and the patient should be operated on either at once or after a more prolonged period of omission of iodine. She is by no means the best operative risk, but will not become better so long as iodine is continued." The patient was taken to a surgical clinic for operation on the morning of April 14. While waiting for the anesthesia to be started, she became somewhat nervous and the pulse rate rose to 176. It did not quiet down under ethylene so Dr. Bevan performed only a

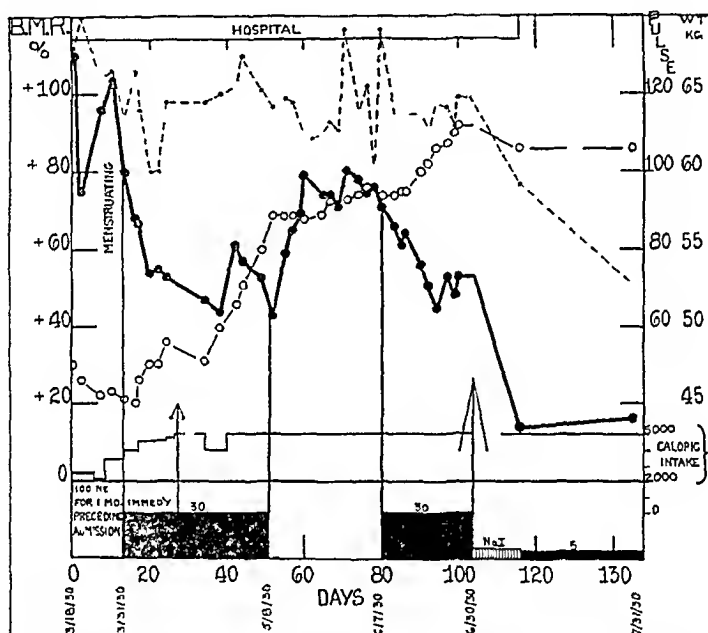


Chart 4 (case 4) —A patient in whom the condition was apparently completely refractory to the administration of 30 drops of compound solution of iodine daily on admission to the hospital after having taken this dose for one month. Partial recovery from refractoriness during a short period of omission of iodine. The small arrow denotes bilateral ligation of the superior thyroid arteries.

bilateral ligation of the superior thyroid arteries and removed an enlarged cervical lymph gland, which was reported to be normal. The postoperative convalescence was uneventful. Following operation the rate of basal metabolism did not change appreciably until after iodine was omitted on May 8. It then rose within fourteen days to a level of from +70 to +80 per cent, accompanied by a decrease in the size and firmness of the thyroid gland and (by May 15) an increase in perspiration, nervousness, emotional instability and the other signs and symptoms of the disease, except exophthalmos. Compound solution of iodine was readministered on June 6, 1930, in a dose of 10 minims three times daily. On the administration of this dose, the rate of the metabolism dropped to a level of about +50 per cent by June 18, and the patient felt much better than during the preceding

administration of iodine, in spite of the fact that the rate of metabolism was not significantly lower. A subtotal thyroidectomy was performed by Dr. Bevan on June 30, and was followed by an uneventful convalescence. The highest post-operative temperature was 101.5 F, and vomiting had ceased within twenty hours.

The gain in weight of 40 pounds (18.1 Kg.) preceding thyroidectomy, part of which occurred during the second period of the omission of treatment with iodine, was the result of the excessive caloric intake (about 5,000 calories most of the time). The excellent physical condition of the patient thus produced, may have been a factor in the uneventful convalescence, as the rate of basal metabolism was as low before the second omission of treatment with iodine as after it was readministered.

Pathologically, the thyroid gland showed changes characteristic of exophthalmic goiter.

Unlike the four preceding cases, operation was performed in the following case when the rate of metabolism was rising rapidly during the administration of iodine. The patient's death from a typical thyroid crisis about forty hours later stands out in striking contrast to the uneventful recoveries in the other cases and illustrates the danger of operation at such a time. This case was similar to the first three cases in that the peculiar nervous manifestations of exophthalmic goiter, including exophthalmos, became worse as the rate of metabolism rose during the administration of iodine. It differed from the other cases in that this rise occurred much sooner after the initial improvement, during the administration of much larger doses of iodine, and was much more rapid, and in that the patient had acute rheumatic fever as well as exophthalmic goiter.

CASE 5—The patient, Mr. H. E. B.⁵ (chart 5), an American laborer, aged 20, single, entered the Massachusetts General Hospital on June 12, 1929, with a typical case of exophthalmic goiter of about seven months' duration. The case was complicated by acute rheumatic fever that had started one week before admission. In spite of the presence of this acute inflammation, he drove by motor car from his home to the hospital, a distance of 112 miles. On admission the patient was nervous and feverish, and his skin was warm and moist. He had marked exophthalmos, a bilateral lid lag and poor convergence. The thyroid gland showed a well marked symmetrical enlargement with a thrill and a marked bruit over it. There was a marked tremor of the fingers. The heart was enlarged to the left, and there was a presystolic thrill and a rough systolic murmur at the apex and an accentuated pulmonary second sound. The right shoulder and left knee were painful on motion, and the left ankle was swollen, warm and tender. The day after admission there was a to-and-fro frictional rub over the base of the heart, muffled sounds at the apex and well marked enlargement. The administration of

5 It was decided that this case should be reported in the "Case Records of the Massachusetts General Hospital" from the standpoint of the combination of rheumatic fever and exophthalmic goiter in the same patient (Mallory, T. B., Means, J. H., and Young, E. L. Exophthalmic Goiter and Acute Rheumatic Fever, Case no. 15472, *New England J. Med.* **201**: 1056, 1929), and that we should report it from the standpoint of refractoriness.

salicylates was begun on the day of admission, and the next day the administration of a compound solution of iodine was started and continued daily thereafter in large doses. The exophthalmic goiter and the rheumatic fever slowly improved, and the temperature dropped from 103.3 F on admission to normal by June 18 and remained practically normal until after operation. Owing to the serious condition of the patient, no attempt was made to determine the metabolic rate until he had improved. The first basal metabolic rate of +40 per cent obtained on June 21,

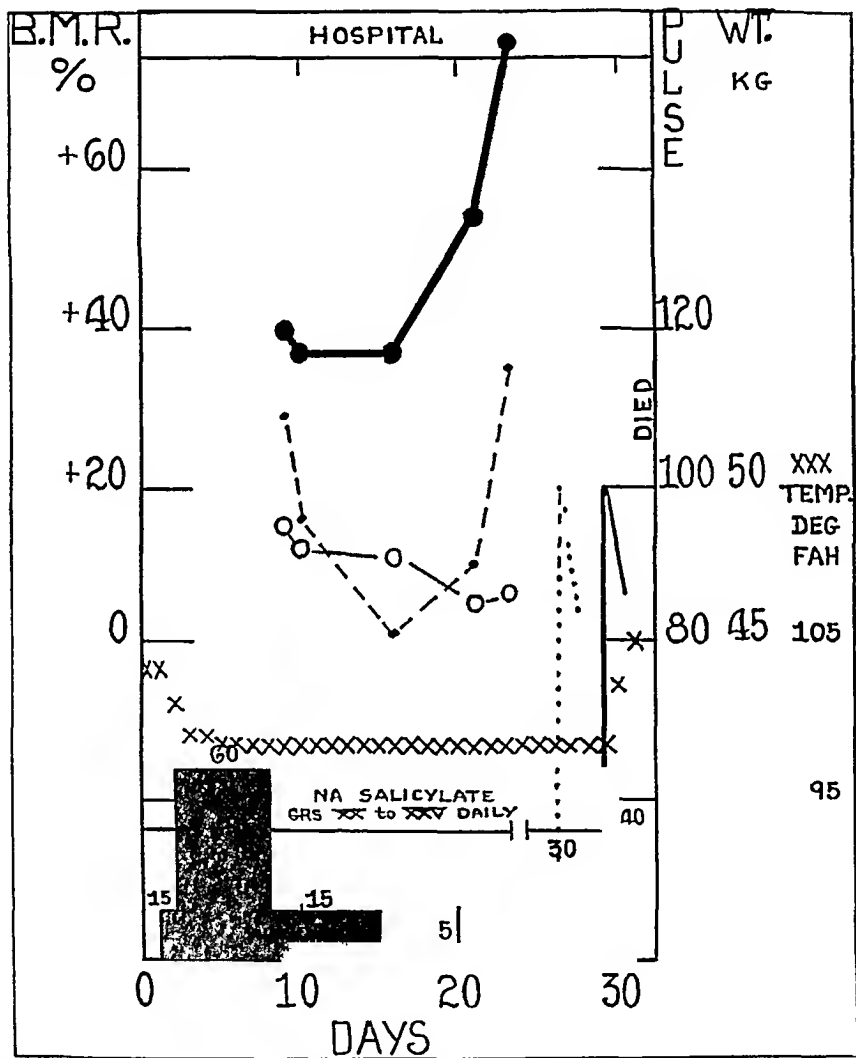


Chart 5 (case 5)—Rapid development of refractoriness to 30 minims of compound solution of iodine administered daily following a short period of improvement. A hemithyroidectomy performed during the period of rising metabolism was followed by a typical thyroid crisis and death in forty hours. Dotted arrow denotes attempt at operation.

therefore represents the level to which iodine reduced it, and judging from the clinical improvement during the administration of iodine the rate of basal metabolism on admission was probably much higher. The metabolism remained at this level until June 28, and, during this time, the clinical improvement in the patient was striking, although the weight decreased slightly. Unfortunately, it was felt

that the patient should not be operated on until sodium salicylate had been omitted long enough to see whether the rheumatic fever was still active. This was not done until July 5. In the meantime, the basal metabolic rate had risen by July 3 to +54 per cent, and there was an exaggeration of symptoms, i. e., he was more nervous and restless and had a wilder look in his eyes. By July 5, the rate of metabolism had risen still further to +76 per cent, and the signs and symptoms of exophthalmic goiter were still more exaggerated. It was decided that operation should be performed at once, and the administration of sodium salicylate accordingly was started again on July 6 after having been omitted for only twenty-four hours. On July 7 the patient was prepared for operation in the usual manner, but on arrival in the operating room the condition was so serious that operation was postponed. The pulse rate was 180 +, and the patient was extremely nervous and tossed about incessantly. He stated that he was not especially worried about the operation and that he was unable to account for his nervousness. He was kept as quiet as possible, and operation was again attempted on July 11. A right hemithyroidectomy was performed in thirty-five minutes. It was thought that he stood the operation fairly well, and his condition was said to be reasonably satisfactory when he returned to the ward. A few hours after operation, however, the temperature was 102 F by mouth and later 103 F by rectum. That night it was 105.3 F by rectum, and it remained at about this level until he died at 12:01 a. m., on July 13. The pulse rate corresponded with the temperature, and after he returned from the operating room it slowly rose from 100 to 153. The next morning it was from 120 to 140 and slowly rose until it was over 200 shortly before death. Following operation he became extremely nervous, he perspired profusely, and he was cyanotic and thrashed about in bed. Putting the patient in an oxygen tent reduced the cyanosis slightly. A few hours before death he became irrational. Compound solution of iodine was given in large quantities by rectal taps after operation, physiologic solution of sodium chloride was given intravenously, by rectum and subpectorally, and dextrose was given intravenously and by rectum. The patient also took a considerable quantity of water and some iodine by mouth.

The mass of thyroid tissue removed at operation weighed 104.5 Gm and on microscopic examination the acini showed "considerable variation in size, the majority being large but only partially distended with colloid." They were "lined by high columnar epithelium showing numerous papillary projections." At autopsy, the thymus weighed 28 Gm, the mesenteric lymph glands and the spleen were slightly enlarged, and the heart showed a healing fibrinous pericarditis, slight fibrous thickening and numerous small translucent granules about the edges of the mitral valve. The lungs showed passive congestion, but evidence of pneumonia was not present.

In this patient, as in the preceding four, the thyroid gland became much firmer when iodine was administered than it was before, and, as in the first three cases, this firmness persisted when the rate of basal metabolism rose during the administration of iodine.

It might be argued that in this patient the basal metabolic rate began to rise only when the dose of the compound solution was reduced from 15 minims (0.9 cc.) daily to 5 minims (0.3 cc.) daily. Because of the small dose of iodine that will produce a maximum effect in exophthalmic goiter,² it seems unlikely that this reduction was responsible for the increase in the rate of basal metabolism. Moreover the

patient received 30 minims (18 cc) daily for five days just before operation, without clinical improvement, and larger doses immediately after operation

The following data are recorded to illustrate that a patient who shows little or no reduction in the rate of basal metabolism during the administration of iodine may improve clinically (prolonged rest presumably being a factor) and have a fairly satisfactory convalescence

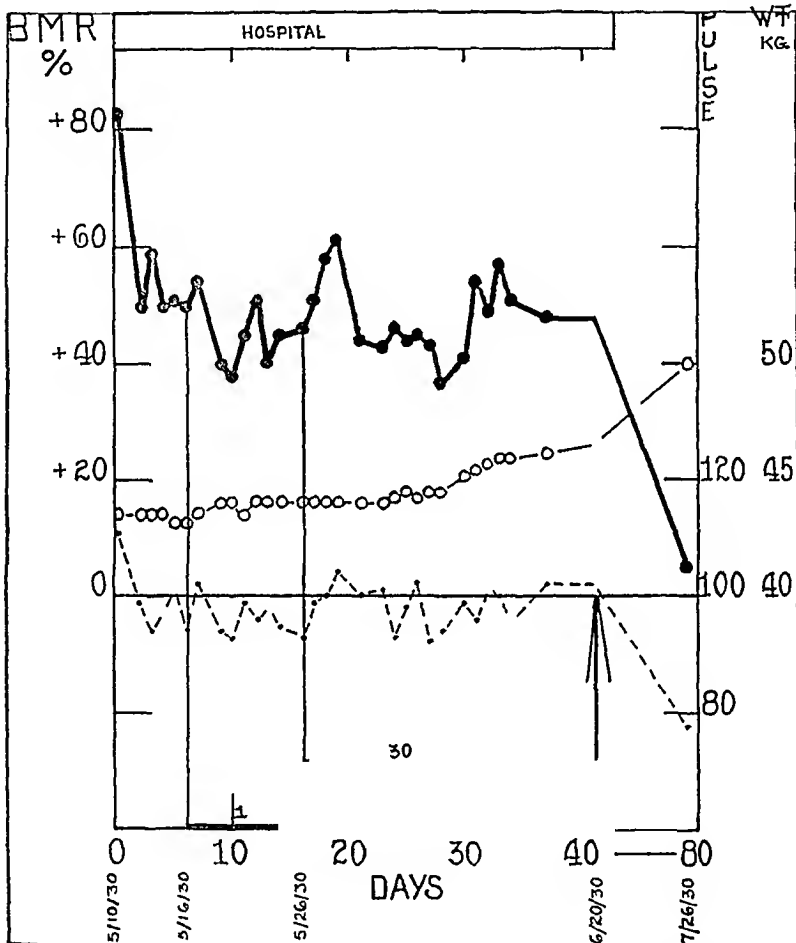


Chart 6 (case 6) —Definite clinical improvement but no reduction in the basal metabolic rate during rest and the administration of iodine in large doses. Subtotal thyroidectomy was followed by only moderate postoperative reaction

from a subtotal thyroidectomy. A few other patients who responded similarly have been observed.

From the standpoint of operative risk, it would appear that a moderately high stationary rate of metabolism during the administration of iodine may be a less serious omen than a rapidly rising rate of metabolism during the administration of iodine.

CASE 6—The patient, Mr W N (chart 6), an American painter, aged 36, entered the Brown service of the Presbyterian Hospital, on May 9, 1930, with a

typical case of exophthalmic goiter of about four months' duration. On admission he was very nervous, restless and emotionally unstable. The skin was warm, moist and somewhat flushed. There was a well marked fine tremor of the extended fingers, well marked bilateral exophthalmos and lid lag, poor convergence and a moderate symmetrical enlargement of the thyroid gland with a systolic bruit all over the right lobe, which was most marked at the superior pole. The day after admission the basal metabolic rate was +83 per cent, but during the test the patient was restless, and this result probably did not represent the true basal metabolic level at that time. Two days later it was +50 per cent, and it remained at approximately this level until after operation. The patient had been using iodized salt for domestic purposes for several years, but he had not had iodine in any other form before admission. The administration of iodine was started on May 16 in a dose of about 6 mg daily, and on May 26 this was increased to about 250 mg daily. During rest in bed and the administration of iodine the patient became less nervous, perspired less, slept better and suffered less from palpitation in spite of no reduction in the rate of basal metabolism. That the improvement was not so marked as it might have been, however, is shown by the following note of June 6: "Still nervous and somewhat erratic. Slight tremor. Exophthalmos persists. Bruit at right inferior pole of thyroid but not elsewhere. Thyroid hard. Well marked palpitation. Perspires freely on warm days. Sleeps well. Little worry. Says he feels '100 per cent better' than on admission. He is, however, still definitely thyrotoxic and by no means the best operative risk. It is questionable whether he should be operated on now or after a period of omission of iodine." Nevertheless, following a subtotal thyroidectomy by Dr E M Miller on June 20, the patient had a satisfactory convalescence. He had the usual amount of fever for five days after operation, the highest point reached being 102 F, and there was a period of auricular fibrillation of a few hours' duration, beginning the day after operation. There was no nausea or vomiting.

PHENOMENA THAT MAY BE RELATED TO REFRACTORYNESS TO IODINE

In addition to temporary improvement during the continuous administration of iodine, the following types of reaction have been observed:

1. When iodine is omitted after producing its usual remission, the rate of metabolism may quickly rise to a higher level than that noted before the administration was started (chart 7 in this article and chart 5 and the case of Mr L O in Starr's⁶ paper).

2. The rise following the omission of iodine may occur abruptly, even when iodine has not produced a reduction in the rate of basal metabolism (chart 8 in this article and charts 7, 8, 9 and 10 in the paper of Starr, Segall and Means⁷).

3. While iodine is being administered, the rate of metabolism may not show an initial reduction, but may rise higher than it was before.

⁶ Starr, P. The Course of Hyperthyroidism Under Iodine Medication, *Arch Int Med* **39** 520 (April) 1927.

⁷ Starr, P., Segall, H N, and Means, J H. The Effect of Iodine in Exophthalmic Goiter, *Arch Int Med* **34**:355 (Sept) 1924.

the administration of iodine was started and higher still when iodine is omitted (chart 9)

4 A dose of iodine which in itself is too small to cause a reduction in the rate of basal metabolism may interfere with the effect of much larger doses administered immediately afterward⁸

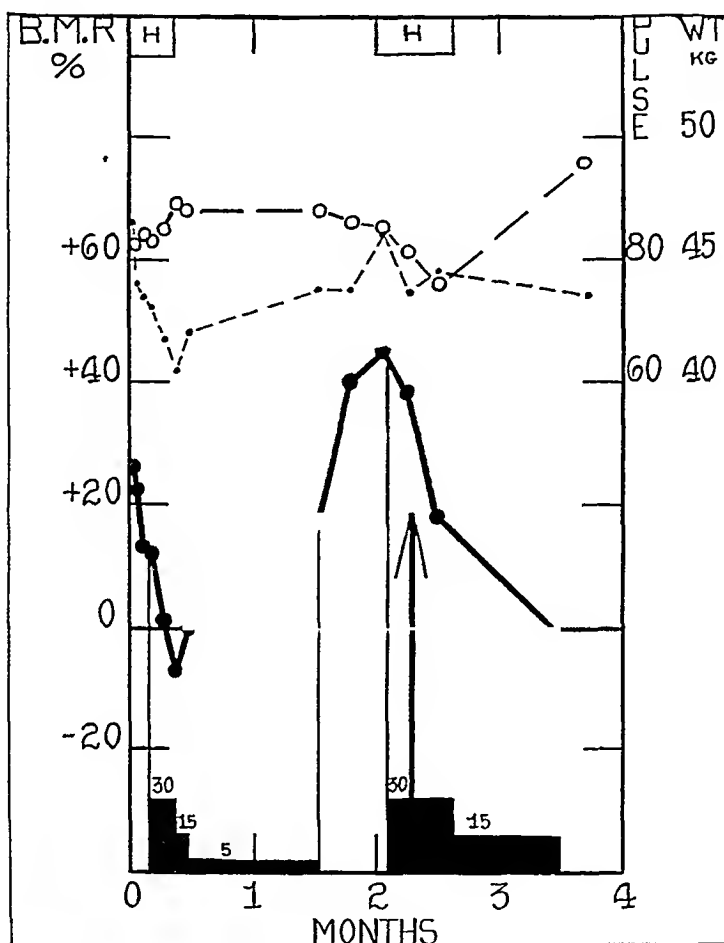


Chart 7 (Mrs A H, lab no 5917) —Omission of iodine after the usual remission (first administration) followed by a rise of the basal metabolic rate to a higher level, and greater severity of the disease than had been present initially (The data recorded in charts 7, 8 and 9 are from the Massachusetts General Hospital)

⁸ Thompson, W O , Thorp, E G , Thompson, P K , and Cohen, A C The Range of Effective Iodine Dosage in Exophthalmic Goiter II The Effect on Basal Metabolism of the Daily Administration of One-Half Drop of Compound Solution of Iodine, *Arch Int Med* 45 420 (March) 1930 Thompson, W O , Cohen, A C , Thompson, P K , Thorp, E G , and Brailey, A G The Range of Effective Iodine Dosage in Exophthalmic Goiter III The Effect on Basal Metabolism of the Daily Administration of One-Quarter Drop of Compound Solution of Iodine and Slightly Smaller Doses, with a Summary of Results to Date, *Arch Int Med* 45 430 (March) 1930

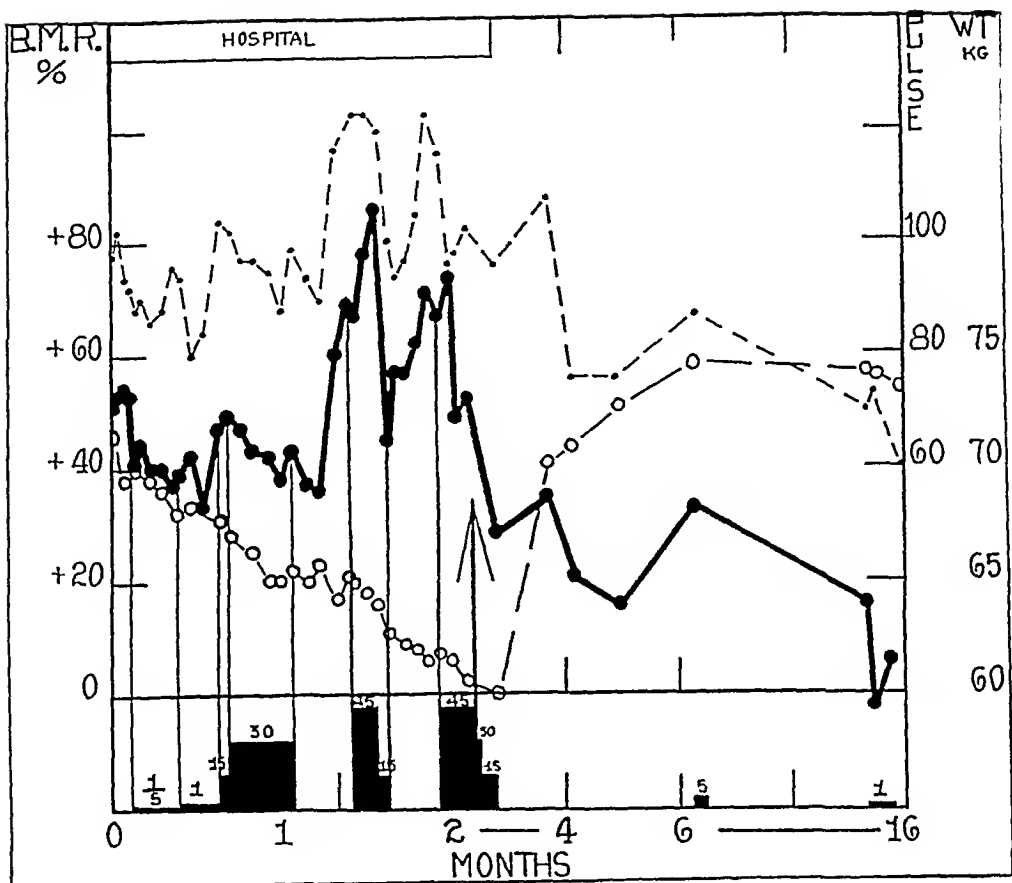


Chart 8 (Miss A W, lab no 5203) —Only slight reduction in either the basal metabolic rate or the severity of the disease during the administration of iodine (first administration), followed by a well marked increase in both factors when it was omitted

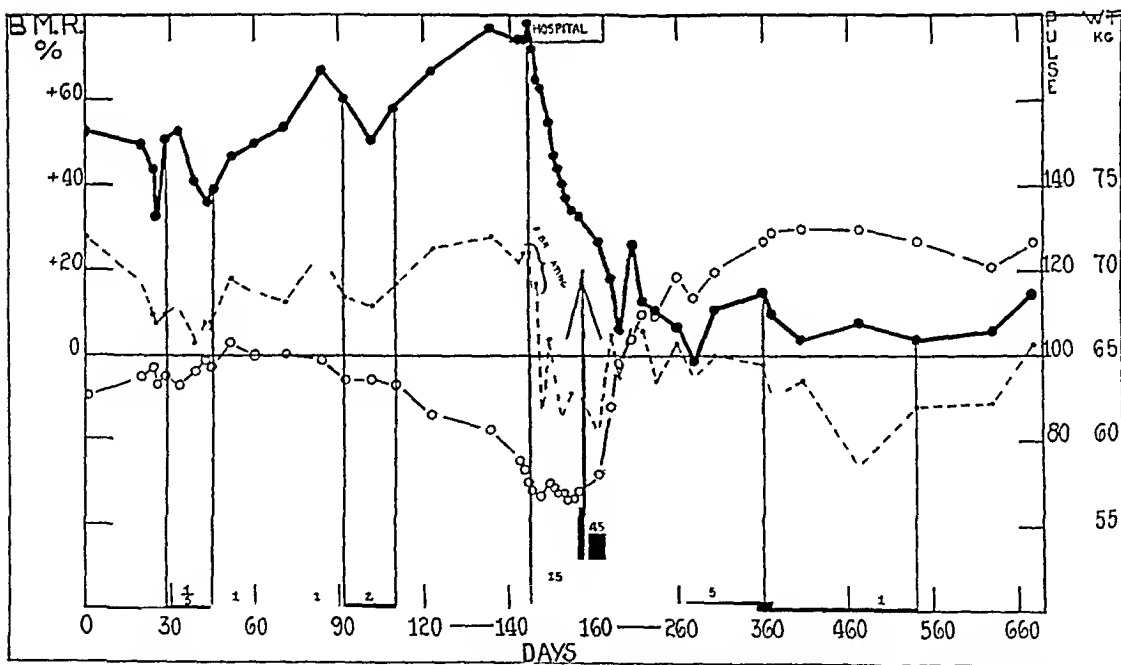


Chart 9 (Miss M K, lab no 5181) —Increase in the basal metabolic rate and severity of the disease during the daily administration of one drop of compound solution of iodine, with still further increase in both factors on the omission of iodine

It is not known in what percentage of cases each of the types of reaction previously described occurs. In the first three, the fact that the rate of metabolism was higher and the intensity of the disease greater following the omission of iodine than they were initially, is analogous to the "postiodine" reaction of Starr (chart 1 in his paper⁹). In the rare instances in which it was possible to make such observations, it was found that this increase in the intensity of the disease following the omission of iodine has usually been of only temporary duration, and has been followed by some spontaneous decrease.⁹

In this connection it is of interest that cases¹⁰ have been reported in which thyrotoxicosis developed during the administration of iodine, although it has never been definitely proved that iodine was the cause of these flare-ups. Occasionally we have seen an increase in the rate of basal metabolism and in the severity of the disease in patients with exophthalmic goiter during the administration of from about 15 to 3 mg of iodine daily, which was followed by a reduction shortly after the dose was increased to 250 mg daily.⁸ In these cases the level to which the large dose depressed the metabolism was, on the average, only slightly lower than the level just before the small doses were started. There may be some truth in the impression of older observers that iodine may aggravate cases of exophthalmic goiter and that latent cases may be lighted up through its use.

TIME REQUIRED FOR DEVELOPMENT OF AND RECOVERY FROM REFRACTORINESS TO IODINE

In case 5, iodine was not omitted, so that it is unknown whether or not the condition was completely or only partially refractory to it. While in case 1 the condition became completely refractory to 1 drop

9 Starr (footnote 6) Goetsch, E. The Use and Misuse of Iodine in the Treatment of Toxic Goiter, New York State J Med **27** 1075, 1927.

10 Kocher, T. Ueber Jodbasedow, Verhandl d deutsch Gesellsch f Chr **39** 396, 1910, Ueber Jodbasedow, Arch f klin Chr **92** 1166, 1910, Discussion on the Surgical Treatment of Graves' Disease, Brit M J **2** 931, 1910. Fleischmann, P. Zur Frage der regional verschiedenen Empfindlichkeit gegen Jod, Munchen med Wchnschr **58** 198, 1911. Trousseau, A. Lectures on Clinical Medicine, translated by P. V. Bazire, The New Sydenham Society, London, lecture 19, vol 1, 1868. Sudeck. Die Jodbehandlung der Schilddrüsenerkrankungen, Klin Wchnschr **2** 1122, 1923. Pineles, F. Ueber die Empfindlichkeit des Kropfes gegen Jod, Wien klin Wchnschr **23** 353, 1910. Jackson, A. S. Iodine Hyperthyroidism, Conclusions Based on a Study of Thirty-Eight Cases, Am J M Sc **170** 271, 1925. Kimball, O. P. Induced Hyperthyroidism, J A M A **85** 1709 (Nov. 28) 1925. Hartsock, C. L. Iodized Salt in the Prevention of Goiter. Is It a Safe Measure for General Use? J A M A **86** 1334 (May 1) 1926. Lahey, F. H. Review of Another Year's Work in Thyroid Disease, Endocrinology **8** 366 1924.

and in cases 2 and 3 only partially refractory to 1 drop and 5 drops, respectively, it must be emphasized that iodine was administered continuously for one hundred and forty-three days in the first case and for only eighty-eight and eighty-seven days, respectively, in the other two. The length of time that elapsed from the beginning of the administration of iodine until the rate of basal metabolism began to rise was not strikingly different in the three cases (from forty-two to fifty-eight days). The rate at which the rise occurred was slightly faster in the last two cases (1 point a day) than in the first case (one-half point a day). A marked difference is noted, however, when these three cases are compared with case 5, in which the rise in the rate of basal metabolism began at least within twenty-one days after the administration of iodine was started, and was very rapid. Owing to the rapidity of the rise and to the rather small number of observations on the basal metabolism, the rate at which it rose can only be approximated, but it could not have taken longer than eight days (from June 28 to July 5) for the basal metabolic rate to rise from $+37$ per cent to $+76$ per cent (39 points). Therefore, it rose at least 5 points a day. The patient had a more severe case of the disease than the other three patients.

In cases 1, 2 and 3, recovery from the refractoriness appeared to be complete after iodine was omitted. At least, in the first and third cases, when the administration of iodine was resumed, the metabolism dropped to as low a level as it had previously done when iodine had been given. The exact length of time required for this recovery is unknown, but it occurred within sixty-four, twenty-four and fifty days respectively in these three patients. The recovery in the third case was complicated by roentgen treatment. In the first case, following the omission of iodine there was some reduction in the basal metabolism and a decrease in the intensity of the disease. In the second case, there was at first a rise in the rate following the omission of iodine and then a reduction which was apparently a result of the change from the daily routine at home to rest in bed in the hospital. In case 4 the rate of metabolism during the readministration of iodine dropped to as low a level after the omission of iodine for fourteen days as after its omission for twenty-nine days.

After the omission of iodine for twenty-seven days in the case summarized in chart 5 of Stair's⁶ paper, the second remission was not as complete as the first. In another case reported by the same author (chart 7 in his paper), a well marked remission occurred after iodine had been omitted for sixty-four days. In chart 4 of the paper by Stair, Segall and Means,⁷ it is shown that after the omission of

iodine for eleven days the second remission was not as great as the first in one case, and was just as great in another. Iodine had been given for only eleven and thirteen days, respectively, before it was omitted and the rate of metabolism rose only to its pre-iodine level when this medication was stopped. Coller¹¹ said "If a recurrence with the continued use of iodine has occurred, there will be an exacerbation of symptoms when iodine is stopped. After a certain length of time has elapsed—the optimum time is not clear—the readministration of iodine will cause another remission."

In some patients refractory to iodine after its prolonged administration, Graham¹² observed a "favorable response" to iodine when its administration was resumed after a period of omission of from three to six weeks.

In case 1, the initial short period of iodization was apparently not associated with the development of refractoriness, whereas the prolonged administration was. When the administration of iodine is begun after a period of omission, the second response is said by some authors to be less marked than the first.¹³ The difference between this observation, on the one hand, and that of Coller¹¹ and ourselves on the other, probably can be accounted for by two factors: (1) Sufficient time may not have been allowed to elapse between the two administrations of iodine.¹⁴ (2) A spontaneous variation may occur in the disease itself.¹⁵

CLINICAL STATUS OF THE PATIENT DURING THE REFRACTORY PERIOD

In cases 1, 2, 3 and 5, as the rate of metabolism was rising during the administration of iodine, all of the peculiar nervous manifestations of the disease not only were present, but were becoming

11 Coller, F. A. The Use of Iodine in the Treatment of Goiter, *Ann Clin Med* **5** 91, 1926.

12 Graham, A. Preoperative Iodine Therapy in Toxic Goiter. Indications and Limitations, *Am J Surg* **2** 354, 1927.

13 Hutton, J. H. Dangers of Iodine in the Treatment of Goiter, *Illinois M J* **50** 408, 1926. Holmes, M. E. The Value and Danger of Iodine in Thyroid Disease, *New York State J Med* **27** 538, 1927.

14 This is perhaps illustrated in chart 7 of the paper by Plummer and Boothby (The Value of Iodine in Exophthalmic Goiter, *J Iowa State M Soc* **14** 66, 1924). There was much less reduction in basal metabolism during the second administration of iodine than during the first. Iodine had been omitted for only eight days, however. During the third administration, after iodine had been omitted for seventy-four days, the response was just as striking as initially. The data are somewhat complicated by ligations but nevertheless illustrate the point.

15 Thompson, Brailey, Thompson and Thorp (footnote 2, second reference).

more intense. When the rate of metabolism finally reached its highest point during the administration of iodine, all of the patients were worse than they had been previously. Their clinical condition was indistinguishable in type from their pre-iodine condition, except that all the signs and symptoms of exophthalmic goiter were more intense. In the second and third cases they became somewhat more intense on the omission of iodine, but in the first case, not only did no further increase occur, but, as stated before, there even occurred a slight spontaneous decrease in the severity of the disease when iodine was omitted. In case 4 after the patient had had 30 drops of the compound solution of iodine daily for one month before entering the hospital, the nervous phenomena of the disease were indistinguishable in type from those in a patient with a severe case of exophthalmic goiter who has never had iodine, and they did not increase in intensity following the omission of iodine. In case 1, the patient's eyes began to be prominent about two months before the omission of compound solution of iodine, and in case 2, about two and one-half weeks before its omission. In both, however, a lid lag was first noticed after the omission of iodine. In case 3, the exophthalmos definitely increased while the rate of metabolism was rising during the administration of iodine, and it appeared to do so in case 5. We have seen an increase in exophthalmos in at least three other patients as the basal metabolic rate was rising during the continuous administration of from about 125 to 250 mg of iodine daily.

SIZE OF THE DOSE OF IODINE

Several good observers are of the opinion that when the administration of iodine is long continued, aggravation of symptoms is more apt to be associated with the administration of large doses than with that of small doses¹⁶. However, we know of no carefully controlled work that has been done to show whether or not a group of patients with exophthalmic goiter is more apt to grow worse during the prolonged administration of large doses of iodine than a similar group during the prolonged administration of small doses. On several occasions we have seen the disease grow worse following a temporary improvement during the continuous administration of small doses (1 drop of the compound solution of iodine daily), just as during the

¹⁶ Neisser, E. Ueber Jodbehandlung bei Thyreotoxikose, *Berl klin Wchnschr* **57** 461, 1920. Fraser, F. R. Iodine in Exophthalmic Goitre, *Brit M J* **1** 1, 1925. Cowell, S. J., and Mellanby, E. Effect of Iodine on Hyperthyroidism in Man, *Quart J Med* **18** 1, 1924. Marine, D. Iodine in the Treatment of Diseases of the Thyroid Gland, *Medicine* **6** 127, 1927.

continuous administration of large doses (30 drops daily¹⁷) Charts 1 and 3 are perhaps examples of this, although the temporary administration of large doses complicates the picture somewhat. We¹⁸ have shown that what are commonly regarded as small doses (from 3 to 5 drops of compound solution of iodine daily) are in reality considerably greater than the minimum amount of iodine that will produce a maximum reduction in basal metabolism in most cases. So far as the cases in this series are concerned, it may be noted that in the first case the temporary administration of large doses (from 30 to 90 drops daily) appeared to accelerate slightly the rate at which the condition became refractory to 1 drop daily. In the second case, it is not known what would have happened to the metabolism had the administration of 5 drops daily been continued and 30 drops not been given, or had 1 drop daily been continued and the larger doses of 5 and 30 drops daily not been given.

A fairly large number of observations published elsewhere¹⁹ suggested that the most important factor in determining the course of the basal metabolism during the prolonged administration of iodine may be the severity of the disease and not the size of the dose of iodine. Thus in mild cases the basal metabolism can often be held at or near the normal level for months to years by the prolonged administration of iodine. On the other hand, severe and moderately severe cases rarely show more than temporary improvement¹⁷. Therefore, refractoriness seems to occur primarily in the moderately severe and severe cases of the disease. The fact that the rate of metabolism began to rise sooner and rose more rapidly in case 5 than in cases 1, 2 and 3 may be attributed to the greater severity of the disease as well as to the larger doses of iodine. Moreover, it is possible that while the acute rheumatic fever that was present on admission to the hospital did not prevent a marked temporary improvement during the administration of iodine, it may have tended to shorten the duration of this improvement.

While the data in this paper demonstrate primarily that complete refractoriness to small doses of iodine may develop, it appears to us probable that complete refractoriness to large doses may also develop. For example, in case 4 the condition was apparently refractory to large doses on the patient's admission to the hospital, that is, after one month's administration. In case 5 the condition became at least partially refractory to large doses, as judged by the marked increase in

17 Thompson, Thompson, Brailey and Cohen (footnote 3, second reference)

18 Footnote 2 Thompson, Thorp, Thompson and Cohen (footnote 8)

19 Thompson, Thompson, Brailey and Cohen (footnote 3) Thompson, W. O., Morris, A. E., and Thompson, P. K. Thyrotoxicosis Following Subtotal Thyroidectomy for Exophthalmic Goiter, *Arch. Int. Med.* **46** 946 (Dec.) 1930

the basal metabolic rate and in the severity of signs and symptoms before operation and the thyroid crisis after operation. Moreover, for some reason that at present is not clear, a small percentage of patients show no response initially to the administration of large doses of iodine.

COMMENT

There are at least two possible explanations of the phenomena observed.

1 Iodine in no way alters the course of the disease, and, during its prolonged administration, the rate of basal metabolism at any point is just what it would have been if the administration of iodine had been started shortly before. In other words, if the condition becomes completely refractory to iodine at a certain time during administration, it would have been completely refractory at exactly the same time if no iodine had been administered, and iodine plays no rôle in the development of the period of refractoriness.

2 It is possible that in some cases during the administration of iodine some reaction to it occurs which tends to counteract its beneficial effects. The period of refractoriness may thus be thought of as an end-result of the reaction to iodine.

At present neither hypothesis can be proved or disproved. There are certain facts that appear to support one hypothesis and certain facts that appear to support the other. In favor of the first are the following observations:

1 A few patients appear to be initially refractory to iodine.

2 In some patients the effect of iodine on the basal metabolism and clinical picture may vary markedly from time to time.²⁰

3 In one mild case of the disease we²¹ observed that the basal metabolism both rose and fell during the continuous administration of iodine under the same conditions of activity.

It was perhaps for similar reasons that Means,²² on the basis of Plummer's hypothesis,¹ was led to say

The "thyrotoxicosis of exophthalmic goiter" may be thought of "as made up of two components, one of which can be held in abeyance so long as an excess of iodine is present, this we may call A, the other of which, influenced by iodine, we may

20 Thompson, Brailey, Thompson and Thorp (footnote 2, second reference) Thompson, Thompson, Brailey and Cohen (footnote 3, second reference)

21 Thompson, Thompson, Brailey and Cohen (footnote 3, second reference), *Myxedema During the Administration of Iodine in Exophthalmic Goiter*, *Am J M Sc* **179** 733 (June) 1930

22 Means, J. H., and Richardson, E. P. *The Diagnosis and Treatment of Diseases of the Thyroid*, Oxford Monographs on Diagnosis and Treatment, New York, Oxford University Press, 1929, vol. 4, p. 150

call B The ratio of the components A B will vary from patient to patient, from place to place, and in the same patient from time to time. As the disease runs its course important changes in the ratio undoubtedly occur, and the relative magnitude of the influence to be had by saturating the patient with iodine will vary accordingly."

In favor of the second hypothesis are the following observations

1 Whereas the reduction in the rate of basal metabolism during the administration of iodine varies considerably from patient to patient, it is usually well marked, and cases that show no reduction are not common, provided iodine has not been administered shortly before. If refractoriness to iodine may be regarded as a stage in the course of most cases of exophthalmic goiter, it seems strange that a larger number of patients are not initially refractory to iodine.

2 As previously mentioned, doses of iodine inadequate to cause any reduction in the rate of basal metabolism may sometimes interfere with the effect of much larger doses administered immediately afterward.

3 When iodine was omitted as the rate of basal metabolism was rising in cases 2 and 3, the response appeared to be recovery from the refractoriness and not a further development to complete refractoriness. At least in the first patient, the refractoriness had disappeared after an interval of twenty-four days. In the second patient, it had disappeared after an interval of fifty days (how much sooner is unknown).

The criticism can always be made that we do not know what the course of the basal metabolism would have been in our cases had iodine never been omitted. For this reason, the natural course of the disease can usually be invoked to explain everything that happens to patients with exophthalmic goiter.

Regardless of what the explanation of these findings may be, our data indicate that the peculiar nervous manifestations of exophthalmic goiter may be present during the administration of iodine in both small and large doses. Thus, in patients with this disease, while iodine is being administered, exophthalmos may first appear or increase, and the remainder of a clinical syndrome that we are unable to distinguish from that of exophthalmic goiter may grow more intense. Lahey²³ reported several cases in patients who came to his clinic in the crisis of the disease and who died before operative procedures could be contemplated in spite of "the most heroic measures," including the administration of iodine in large doses. This has some bearing on the treatment for the disease. For example, it is sometimes claimed that the height of the basal metabolic rate is not a criterion of the operative

23 Lahey, F. H. The Management of Goiter, *J. Indiana M. A.* **23** 117, 1930

risk of the patient and that, so long as iodine is being administered in excess, the patient is a good risk, regardless of what happens to the rate of basal metabolism. The reason given for this is that operative mortality is bound up primarily with the "bad product" (i.e., component A) and not with the "good product" (component B), and, on theoretical grounds, the "bad product" is said to be always completely under control during the administration of iodine in excess. While it is true that the height of the rate of basal metabolism is not the only criterion for determining the risk, the last part of this claim seems questionable. For example, when the patient in case 5 was first brought to the operating room, he behaved as patients with severe cases of the disease did in similar circumstances before the days of the use of iodine, and operation had to be postponed. When operation finally was performed, however, he had a typical postoperative crisis, with marked nervousness, vomiting, fever, tachycardia and delirium, resulting in death. This postoperative reaction was indistinguishable from that presented by patients with severe cases of the disease before iodine was used for treatment.

We have occasionally seen similar postoperative reactions which were not fatal in patients who had received iodine in large doses for only the usual time before operation (from ten to fourteen days), notably in those who had not responded very well to it, but also in patients who had shown a satisfactory response. The reactions to which we refer are characterized by marked nervousness, thrashing about in bed, a wild expression in the eyes, fever, marked tachycardia and occasionally delirium, vomiting and auricular fibrillation, and we are unable to distinguish them from those that occurred before the days of treatment with iodine. Lahey²⁴ and Clute²⁵ reported severe postoperative reactions, some of which were fatal, in patients who had been given iodine in large doses both before and after operation. De Courcy,²⁶ Dunhill,²⁷ Graham¹² and Kessel and Hyman²⁸ expressed the belief that some patients remain poor operative risks in spite of

24 Lahey, F. H. The Use of Iodine in Goitre, Boston M. & S. J. **193** 487, 1925, The Management of Post-Thyroidectomy Complications, S. Clin. North America **8** 13, 1928.

25 Clute, H. M. Effect of Compound Solution of Iodine and Rest in Surgery of Exophthalmic Goiter, J. A. M. A. **86** 105 (Jan. 9) 1926.

26 De Courcy, J. L. Review of 3,600 Thyroidectomies, Am. J. Surg. **2** 225, 1927.

27 Dunhill, T. P. Toxic Goitre, Brit. J. Surg. **17** 424, 1930.

28 Kessel, L., and Hyman, H. T. Exophthalmic Goiter and the Involuntary Nervous System. XVI. The Influence of Subtotal Thyroidectomy With and Without Compound Solution of Iodine on the Course of the Disease, Arch. Int. Med. **40** 623 (Nov.) 1927.

preparation with iodine While one of the chief benefits of iodine has been a marked decrease in the number of postoperative crises, the fact that iodine has been administered in large doses for ten days or more before operation is in itself not an absolute guarantee that there will not be one

It may thus be said that regardless of the theoretical interpretation of these phenomena, they suggest the following therapeutic applications 1 In severe cases of the disease, operation should be performed as soon as the metabolism reaches a level during the administration of iodine, because the beneficial effects in such cases may be of short duration 2 If in such cases, however, operation is slightly delayed and the rate of metabolism starts to rise rapidly soon after the initial drop, operation should not be performed until iodine has been omitted for a short time, because in the presence of a rapidly rising rate of metabolism operation appears to be unsafe A short period of omission of iodine may cause the refractoriness to disappear and make the patient a better operative risk

Most observers have seemed loathe to omit iodine if the rate of metabolism is rising This attitude is based on the rather widespread belief that the effect of iodine never completely wears off while it is being administered, regardless of what happens to the basal metabolism Our observations suggest that in such a stage of the disease the patient may be largely refractory to iodine, that its continued administration may be associated with a still further increase in the severity of the disease, that the rate of metabolism may not rise much higher following its omission, and that its omission may be followed by the disappearance of the refractoriness During the period in which iodine is omitted, the patient should be at rest in bed Medication probably does not need to be discontinued longer than from three to four weeks Iodine may then be readministered, and if the basal metabolism drops, operation may be performed with comparative safety

Campbell,²⁹ Graham,¹² De Coucy²⁶ and Goetsch³⁰ expressed the belief that operation on a patient who shows a high rate of metabolism and who is very ill after the prolonged administration of iodine may cause death Campbell is of the opinion that after a short period of freedom from iodine, such patients again respond to it and become good operative risks It is said to be the custom at the Toronto General Hospital to omit iodine for a short time in all such cases³¹

29 Campbell, W R Personal communication to the authors

30 Goetsch (footnote 9)

31 Graham, D Personal communication to the authors

In our series there is a contrast between the patient in case 5, who was operated on while the metabolic rate was rising rapidly during the administration of iodine and who died from a typical postoperative crisis, and the first four patients, in whose cases iodine was omitted when the metabolic rate was rising or was very high and who were not operated on until the refractoriness to iodine had disappeared, when convalescence was uneventful. It would perhaps have been preferable to have regarded the goiter in case 5 as the major problem and to have proceeded with the operation without waiting to determine whether the rheumatic fever would recur when salicylates were omitted. Since this was not done, it would seem that operation should have been postponed until iodine had been omitted for a short time.

In cases of the disease that are only moderately severe, it is our impression that the rate of metabolism usually remains depressed for several weeks before starting to rise, and that the rise is usually slow. In this type of case we doubt that any harm is done by delaying operation for a short time while iodine is being administered. Furthermore, we doubt that a very slowly rising rate of metabolism during the administration of iodine is a contraindication to operation, unless the metabolism has already attained a high level. It is also true that the severity of the postoperative reaction cannot be predicted entirely by the preoperative height of the rate of metabolism. Some patients who show little or no reduction in the rate during the administration of iodine have only moderate postoperative reactions (case 6). Like all other biologic phenomena, the response of patients with exophthalmic goiter to iodine is variable.

SUMMARY AND CONCLUSIONS

During the prolonged continuous administration of iodine one patient with exophthalmic goiter, after showing a remission, became completely refractory to 6 mg. of iodine daily, a dose that was at other times sufficient to produce a maximum reduction in the basal metabolism. Four other patients became at least partially refractory to iodine during its prolonged administration in doses of from 6 mg. to 250 mg. daily.

In four of the preceding five cases, iodine was omitted and the refractoriness disappeared.

The fifth patient was operated on when the metabolism was rising rapidly during the continuous administration of iodine, and he died about forty hours afterward from a typical postoperative crisis. This reaction was indistinguishable from those previously seen in patients who were operated on without receiving iodine.

The exact length of time necessary for the refractoriness to disappear completely when iodine is omitted is unknown, it was observed to do so within twenty-four days

When the metabolism reached its highest point during the administration of iodine, the disease was more severe than it had previously been, and all the peculiar nervous manifestations not only were present, but were more intense. In two patients, exophthalmos was first noted as the rate of metabolism was rising during the continuous administration of small doses of iodine, and in the other two, it became more marked under these circumstances

The reactions appear to be more characteristic of severe cases than of mild cases

Our observations do not appear to support the hypothesis that the peculiar nervous manifestations of exophthalmic goiter are always under control as long as an excess of iodine is being administered

In severe cases operation should be performed as soon as a maximum reduction in the rate of basal metabolism occurs

In any case, when the metabolism has increased markedly during the administration of iodine, it is probably wise to postpone operation until after this medication has been omitted for from three to four weeks, with the patient at rest in bed, to allow the refractoriness to disappear, and until the administration of iodine has been resumed

Certain phenomena that may be related to the development of refractoriness to treatment with iodine are described

CONGESTIVE HEART FAILURE

X THE MEASUREMENT OF VENTILATION AS A TEST OF CARDIAC FUNCTION *

T R HARRISON, M D

F C TURLEY, M D

EDGAR JONES, M D

AND

J ALFRED CALHOUN, M D

NASHVILLE, TENN

In the examination of the heart, various methods are employed. Most of them are of value, but none of them afford an accurate index as to the functional capacity of the heart. The most commonly employed method of estimating the functional capacity consists in counting the pulse before and after standardized exercise. Concerning such tests, Sir James Mackenzie¹ stated:

One of the most profitless lines of investigation has been those numerous and elaborate attempts to discover the condition of the heart's efficiency by various tests in which bodily effort is employed and the heart rate taken as a standard.

With regard to the measurement of cardiac capacity for work, Sir Thomas Lewis² said:

Innumerable tests have been, and continue to be devised to answer this question, they are based mainly upon pulse and blood pressure readings. Experience of such tests have convinced me that they have little practical value, and tending as they often do to become rules of thumb, they likewise become most undesirable.

Our own experience with the pulse rate test has not been extensive. In the majority of instances patients with cardiac disease exhibit a greater and more prolonged increase than normal persons after performing the same exercise, but the exceptions to this rule are so frequent as to make the method of little value. Examples of these exceptions are shown in table 1. The exercise was carefully standardized. With mild exercise, the response of the normal subject and of the patient with advanced cardiac disease were practically identical. After more severe effort, the patient with early organic cardiac disease returned to normal quicker than did either the normal subject or the one with cardiac neurosis.

* Submitted for publication, Nov 8, 1930.

¹ From the Department of Medicine of Vanderbilt University, Nashville, Tenn.

¹ Mackenzie, James. Diseases of the Heart, ed 4, London, Oxford University Press, 1925, p 114.

² Lewis, Thomas. Early Signs of Cardiac Failure of the Congestive Type, Brit M J 1 849, 1930.

Most clinicians would agree that at the present time there is only one reliable index to cardiac function and that this is the degree of dyspnea during and after effort. But dyspnea is a subjective phenomenon and hence as such cannot be expressed accurately in quantitative terms. The present research is concerned with an effort to arrive at a quantitative concept of dyspnea by means of respiratory measurements. Most of our present knowledge along these lines has come from the important studies of Francis W. Peabody and his co-workers,³ and the present study is in large measure based on the fundamental concepts developed by them.

METHOD

In general, the method first employed consisted of measuring the amount of air expired by the subject during a period of standardized exercise and for a certain period after the exercise was ended. The apparatus used is shown in

TABLE 1—*The Pulse Rate After Exercise*

Subject	Clinical Data	Pulse Rate								Comment
		Before Exercise	1 Min	2 Min	3 Min	4 Min	5 Min	6 Min	7 Min	
W G H	Normal	88	100	92	90	88	90	90	88	Mild exercise
E G	Syphilis, aortic insufficiency, has had three breaks in compensation	82	96	88	86	84	82	80	80	
W G H	Normal	88	141	134	124	112	106	104	102	Severe exercise
R L M	Cardiac neurosis	106	152	134	126	126	122	114	116	
V B M	Hypertension, slight cardiac hypertrophy, no congestive cardiac failure	104	144	120	112	106	108	104	106	

figure 1. A platform 64 cm broad was supported at each side by two steps, each 16 cm high. The subject wore a mask with inlet and outlet valves. The outlet valve was connected by means of flexible rubber tubing with a two-way trap, which in turn was connected with two Tissot spirometers. The expired air was collected in one spirometer during the exercise and in the other after the exercise. (It happened that a very large spirometer was not available and hence we used two smaller ones. A gas meter would serve the purpose equally well and has the advantage of being cheaper.)

In each instance the duration of the exercise was two minutes. At the end of this period the subject rested quietly in a comfortable chair for five minutes, during which time the ventilation was measured. This time is designated as the "after period." Four different rates of exercise were used. The mildest type consisted of six "round-trips" (i.e., over the steps and back) in two minutes. The others consisted of twelve, sixteen and twenty-four "round-trips," respectively, in two minutes. The operator counted with a stopwatch in order to

³ Peabody, Francis W., et al. Clinical Studies of Respiration, Arch Int Med 10: 846 (Nov.), 955 (Dec) 1915, 20: 433 and 443 (Sept.), 468 (Oct) 1917, 28: 501 (Nov) 1921, 29: 236 (Feb), 277 (March) 1921.

assure that the rate of performance remained relatively constant. For purposes of brevity, the graded exercises will be referred to in the remainder of this paper as, in order of increasing severity, exercise I, II, III and IV, respectively. Exercise I is extremely slow and can be performed by any patient who is able to get out of bed. Exercise II is approximately equivalent to walking at an ordinary pace, and exercise III to rapid walking. Exercise IV is about as severe as a rather slow run. Normal subjects experienced little or no dyspnea with the first three grades, but were slightly to moderately dyspneic toward the end of exercise IV. Exercise IV is rather too severe for any subjects except normal persons.

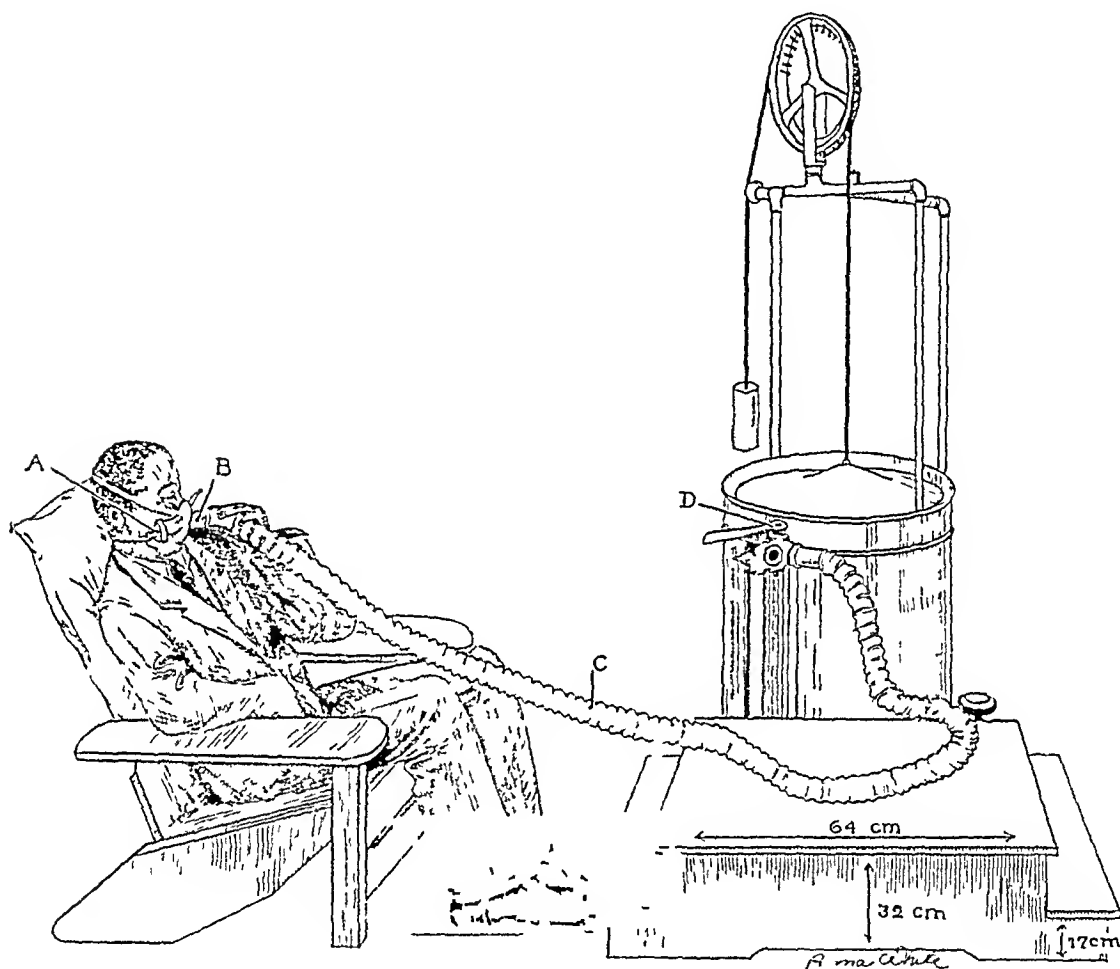


Fig 1—The subject inhales through the inlet valve *A*, and exhales through the expiratory valve *B*. By means of the flexible corrugated rubber tubing *C*, the expired air passes through the three-way tap *D*. During the preliminary rest period, the expired air passes back into the room. At the beginning of the first exercise, the tap is turned, and for the two minutes of the exercise and the succeeding five minutes of the after period the expired air is collected in the spirometer, and the total volume for the seven minute period is measured. The tap *D* is then turned to room air and the spirometer emptied. In like manner the measurements for exercise II and III are made. Although we used a spirometer, a gas meter will serve the purpose equally well and is cheaper.

and patients with very early cardiac disease. After reviewing all of our data we do not believe that the additional information gained from exercise IV is of sufficient value to warrant the additional time and the respiratory discomfort involved.

Consequently, we have decided to employ only exercises I, II and III in our future work

The usual plan consisted of beginning with exercise I, and then, after the usual five minute after period, having the subject perform exercise II, followed by the after period, and so on. However, when one degree of exercise produced moderate or severe respiratory distress, the succeeding grades of work were not done

An attempt was made to evaluate the degree of dyspnea in each instance. Such evaluation is extremely rough and subject to great inaccuracies, but as a rule the observation of the patient's facial expression, alertness and type of respiratory movements, when coupled with his own statement allowed one to judge whether distress was absent, slight, moderate or severe. In the majority of subjects the objective signs of distress as recorded by the operator of the experiment agreed fairly well with the person's statement concerning the dyspnea. However, patients with cardiac neurosis usually complained of more dyspnea than their objective states indicated.

In the first experiments an attempt was made to separate the excess ventilation due to the exercise from the total ventilation. This was done by measuring the ventilation during resting before the exercise and subtracting this value from the ventilation during and after the exercise. However, it was seen that although ventilation during and after a given exercise was fairly constant in the same person from day to day, the ventilation during resting varied rather markedly, and a large error was introduced. (This disadvantage can be overcome by the use of fore periods of one-half hour or more, but in such cases the subject becomes tired of the mask and is likely to be restless.) For this reason the fore period was abandoned, and calculations were made on the basis of the ventilation during the two minute period of exercise plus that during the five minute after period. Such a method of calculating the results has the disadvantage of expressing the values in terms of ventilation for the entire seven minute period rather than per minute, as is customary. However, the after period is necessary, as a large fraction of the excess ventilation comes after, not during, the exercise, particularly in dyspneic subjects. To divide the total amount of ventilation by 7 and call this value ventilation per minute would be absurd, because the actual ventilation varies from minute to minute, being greatest during the second minute of the exercise and the first minute thereafter. Therefore, it is important to remember that the figures reported are arbitrary in the sense that they are obtained for a selected exercise, performed at a chosen rate for a given time.

In order to compare one subject with another, the height and weight of each subject were taken, the surface area was calculated from the Du Bois chart, and the values were expressed in terms of liters per square meter.

The vital capacity was also determined in each subject and expressed in terms of liters per square meter. The reasons for this will be given.

In calculating the values the customary method of reducing ventilation volume to liters at standard conditions has been followed. The values for vital capacity have not been corrected but have been calculated, as is usual in respiratory experiments, for the prevailing temperature and barometric pressure.

RESULTS

The Relation of Dyspnea to Respiratory Measurements—The Variation of the Ventilation. Duplicate observations on six normal subjects are shown in table 2, the values being expressed in terms of liters per square meter. It can be seen that the maximum variation in the same

subject performing the same exercise on different days is 15 per cent, but that the usual variation is considerably less than 10 per cent. Different subjects vary by 20 per cent or more in their ventilations per square meter for the same exercise. The greatest variations occurred in exercise IV, which is sufficiently severe to make the question of the degree of muscular training important. For this reason, as well as for others, this part of the test can well be omitted.

The Correlation between Dyspnea and the Ventilation per Square Meter. The data in table 3 are based on 304 tests and point to a defi-

TABLE 2—Duplicate Measurements of the Ventilation During and After Test Exercises

Subject	Date	Ventilation per Square Meter, Liters				Percentage Difference, Liters				Sex
		For Exercise I	For Exercise II	For Exercise III	For Exercise IV	For Exercise I	For Exercise II	For Exercise III	For Exercise IV	
		I	II	III	IV	I	II	III	IV	
M H	6/18/30	36.0	44.9	48.5	85.4					Female
	6/24/30	35.4	43.7	49.1	75.5	1.6	2.7	1.2	13.6	
M M T	6/17/30	37.6	43.7	55.9	76.4	14.0	5.1	8.8	6.3	Female
	6/20/30	42.9	46.0	51.3	81.3					
E C	6/17/30	34.4	40.9	52.8	83.8	5.7	1.5	3.8	5.6	Female
	6/24/30	36.4	41.5	50.8	79.2					
J A C	6/15/30	36.6	45.7	53.9	74.2	1.6	2.3	6.3	13.2	Male
	7/16/30	36.0	44.6	59.5	65.5					
F C T	6/19/30	39.9	45.7	55.8	74.7	8.6	7.7	15.0	10.6	Male
	7/24/30	36.7	42.4	48.5	67.5					
T R H	6/15/30	41.2	46.7	59.1	83.5	2.5	5.0	5.2	4.5	Male
	6/21/30	42.2	44.4	56.1	79.9					

TABLE 3—The Relation Between Dyspnea and the Ventilation Per Square Meter

Number of Tests	Degree of Dyspnea	Ventilation per Square Meter, Liters								
		Less Than 30	30 to 40	40 to 50	50 to 60	60 to 70	70 to 80	80 to 90	90 to 100	More Than 100
179	None	0	41	97	39	2	0	0	0	0
84	Slight (+)	0	4	7	25	23	14	11	0	0
41	Moderate (++)	0	0	2	5	9	10	8	6	1
16	Severe (+++)	0	0	0	1	4	3	5	1	2

nite relationship between the amount of ventilation and the degree of distress. For instance, it can be seen that when the ventilation per square meter was above 60 liters, dyspnea of some degree almost invariably occurred. However, there is little evidence from the table to indicate whether the probabilities are that any level of ventilation between 60 and 90 liters would be associated with slight, moderate or severe dyspnea. It is evident that the ventilation per square meter is a poor index to the severity of dyspnea.

The Relation of Vital Capacity to Dyspnea. As has been stated, our interest was in dyspnea as such rather than in ventilation. It was soon learned that subjective respiratory distress was not directly proportional to ventilation per square meter. Thus, patients with abnormal

TABLE 4—*The Relation of Diminished Vital Capacity to Dyspnea*

Subject	Date	Diagnosis	Vital Capacity per Square Meter, Liters	Exercise I				Exercise II				Exercise III				Exercise IV			
				Ventilation per Square Meter, Liters		Vital Capacity		Ventilation per Square Meter, Liters		Vital Capacity		Ventilation per Square Meter, Liters		Vital Capacity		Ventilation per Square Meter, Liters		Vital Capacity	
				Dyspnea				Dyspnea				Dyspnea				Dyspnea			
I C T	6/19/30	Normal	2.36	39.9	0	16.9		45.7	0	19.4		53.9	0	23.6		74.7	+	31.7	
	8/ 4/30	With tight binder around chest and abdomen	1.93	36.6	0	19.0		48.9	0	25.3		49.3	+	25.6		78.6	++	40.7	
T R H	6/21/30	Normal	2.53	42.2	0	16.5		44.4	0	17.4		61.1	0	22.0		79.9	+	31.4	
	8/ 4/30	With tight binder around chest and abdomen	1.99	40.6	0	20.4		48.5	0	24.3		52.8	+	26.7		76.8	++	38.6	
A B	8/20/30	Pneumothorax	1.62	40.8	0	25.2		46.2	+	28.6		54.4	+	33.5					
E J	7/14/30	Scotiosis	1.78	40.4	0	25.4		49.1	+	31.0		58.1	+	30.8		79.1	++	50.1	

lungs may have a normal ventilation per square meter and yet be distinctly more dyspneic than a normal person. In table 4 are shown values on two normal subjects with and without tight canvas binders wrapped around their chests and abdomens. Although the vital capacities were reduced only about 10 per cent, the subjects experienced definitely more than their usual discomfort with the severe exercises. Both of these subjects performed the test on numerous occasions under various conditions, and the statements as to the dyspnea are probably reliable. However, the relation of vital capacity to dyspnea is brought out more clearly in the last two subjects in table 4. These persons had abnormally low vital capacities owing to disease. For the various exercises their values for ventilation per square meter were almost exactly the same as those of the two normal subjects, but their distress was definitely greater.

TABLE 5—*The Relation Between Dyspnea and the Ratio $\frac{\text{ventilation}}{\text{vital capacity}}$*

Number of Tests	Degree of Dyspnea	Ventilation							Vital Capacity	Comment
		Less Than 15	15 to 25	25 to 35	35 to 45	45 to 55	55 to 65	More Than 65		
163	None	5	127	47	0	0	0	0		Only 9 tests above 30, 94 per cent of tests below 30
84	Slight (+)	0	5	52	22	5	0	0		No test below 20, 50 per cent of tests between 25 and 40
41	Moderate (++)	0	0	5	21	12	3	0		No tests below 30, 80 per cent of tests between 35 and 55
16	Severe (+++)	0	0	0	1	5	5	5		Three tests below 50, 80 per cent of tests above 50

These observations are confirmatory of the studies of Peabody,³ who pointed out the great importance of decreased vital capacity in the production of dyspnea.

The Correlation between the Ratio $\frac{\text{ventilation}}{\text{vital capacity}}$ and the Degree of Dyspnea. The data in table 4 are in agreement with general clinical experience that, roughly speaking, dyspnea is directly proportional to ventilation and inversely proportional to vital capacity. The ratio $\frac{\text{ventilation}}{\text{vital capacity}}$ should therefore be a better index of respiratory distress than ventilation alone. That this is actually the case is shown by a study of table 5, and a comparison of it with table 3. The total ventilation (for the seven minute period) divided by the vital capacity was compared with the degree of distress in 304 tests on more than 40 subjects (including normal persons and subjects with pathologic conditions who performed exercises of varying severity). Observations on subjects with cardiac neurosis and on persons with respiratory obstruction were omitted from this tabulation for reasons that will be men-

TABLE 6—The Effect of Respiratory Resistance on the Ventilation

Subject	Date	Experimental Condition	Series I				Series II				Series III				Series IV			
			Ventilation per Square Meters	Dyspnea Meters	Vital Capacity	Ventilation per Square Meters	Ventilation per Square Meters	Dyspnea Meters	Vital Capacity	Ventilation per Square Meters	Ventilation per Square Meters	Dyspnea Meters	Vital Capacity	Ventilation per Square Meters	Dyspnea Meters	Vital Capacity	Ventilation per Square Meters	Dyspnea Meters
P. C. T.	6/19/30	Normal, vital capacity 2.38 liters per square meter	39.9	0	16.9	15.7	0	19.1	55.5	0	23.6	71.7	1	11.7				
	8/5/30	Inspiration and expiration valves occluded by corks with holes 1 mm in diam eter, vital capacity 2.21 liters per square meter	33.8	0	11.7	38.9	1	17.1	16.7	1	20.9	67.0	1	30.0				
T. R. H.	6/15/30	Normal, vital capacity 2.55 liters per square meter	41.2	0	16.2	16.7	0	18.1	59.1	0	21.2	81.5	1	32.7				
	8/5/30	Inspiration and expiration valves occluded by corks with holes 1 mm in diam eter, vital capacity 2.56 liters per square meter	36.7	0	11.3	42.5	1	16.6	51.4	1	20.1	71.9	1	28.1				

tioned later. The clinical note as to the maximum degree of dyspnea experienced during the test was recorded before the respiratory measurements were completed. "No dyspnea" was recorded in 163 instances. In none of these was the ratio $\frac{\text{ventilation}}{\text{vital capacity}}$ above 35, and in only 9 observations was this quotient greater than 30. When "dyspnea +" was recorded, the ratio was between 25 and 40 in 65 of the 84 instances, being below 25 in only 5 cases. Moderate (++) dyspnea was usually associated with a quotient of from 35 to 55, and values above the latter level were rare except in patients who seemed to be in severe distress. When one considers the great difficulty and the obvious high percentage of error in classifying the degree of dyspnea, it seems that this ratio is a fairly accurate expression of respiratory distress.

The Importance of the Nutritional State. One naturally expects obese persons to show greater ventilation than other subjects for a given exercise. As a corollary, one wonders whether thin people have less ventilation. In order to study these matters, observations were made on 16 healthy subjects. Their "ideal weights" were calculated according to the formulas

Ideal weight for males=110 pounds for 5 feet and $5\frac{1}{2}$ pounds for each additional inch

Ideal weight for females=100 pounds for 5 feet and 5 pounds for each additional inch

Five subjects were more than 10 per cent overweight, 6 were within 10 per cent of their theoretical ideal weight, 5 were more than 10 per cent underweight. The vital capacity per unit of body surface was least in the obese group and greatest in the normal group.

The values for $\frac{\text{ventilation}}{\text{vital capacity}}$ were considerably higher for the obese subjects and tended to be a little lower in the undernourished subjects than in the group with a more normal nutritional status. The data are shown in table 7.

Such a comparison obviously puts the obese subject at a disadvantage, because his vital capacity is likely to be somewhat subnormal, and since he does more work with the exercise one would expect his ventilation to be somewhat higher. It is true that on the whole he is more dyspneic and therefore the value $\frac{\text{ventilation}}{\text{vital capacity}}$ which, as we have shown, is proportional to dyspnea, should be higher. However, for purposes of comparison with persons suffering from disease, it is desirable to have standards that will reflect the degree of dyspnea due to disease, rather than the dyspnea due to the nutritional state. Therefore, an attempt was made to recalculate the values in such a way as to eliminate the rather marked variation dependent on the body weight. The results of the first attempt at correcting for body weight are shown

in the right hand portion of table 7 These values were obtained by the product of $\frac{\text{ventilation}}{\text{vital capacity}} \times \frac{\text{ideal weight}}{\text{actual weight}}$ By such a method of calculation, the obese subjects have the lowest values and the thin subjects the highest If this method of calculation is adopted, the fat people are more efficient than the subjects with normal nutritional status This is illogical One must remember that the test includes a two minute period of exercise plus a five minute after period The total ventilation is composed of two factors (1) a ventilation during resting that is proportional to metabolism and hence to body surface, and (2) an excess ventilation due to work done, and hence proportional not to body surface but to body weight Therefore, it seems logical to assume that

TABLE 7—The Relation of the Nutritional State to the Ventilation

Sub ject	Height, Inches	Weight, Pounds	Vital Capac- ity per Square Meter, Liters	Ventilation				Ventilation				Ideal Weight		Com ment
				Vital Capacity				Vital Capacity				Actual Weight		
				Exer cise I	Exer cise II	Exer cise III	Exer cise IV	Exer cise I	Exer cise II	Exer cise III	Exer cise IV			
J W H	71 0	218	2 09	18 6	20 9	26 3	39 0	14 5	17 4	20 5	30 4	More than 10 per cent over weight		
E C H	62 0	144	1 92	20 0	21 3	25 6	46 0	16 3	17 5	21 0	37 8			
W G H	67 5	187	1 93	19 3	25 5	28 4	42 3	15 6	20 6	22 9	34 2			
E P C	71 5	205	1 90	23 1	26 5	32 7	40 5	19 6	22 4	27 6	34 2			
G E C	68 0	198	1 99	19 5	22 1	26 6		15 2	17 3	20 8				
Average			1 97	20 1	23 3	27 9	42 1	16 2	19 0	22 6	30 2			
J A C	67 5	145	2 37	15 1	18 8	22 7	29 0	15 7	19 6	23 6	30 2	Within 10 per cent of ideal weight		
T R H	66 5	146	2 55	16 4	17 9	21 9	31 2	16 4	17 9	21 9	31 2			
F C T	69 5	150	2 36	16 4	18 8	22 2	30 4	17 6	20 1	23 8	32 6			
J G M	70 0	172	2 19	18 7	20 4	24 4	38 4	17 9	19 6	23 4	36 9			
W J E	67 5	139	2 42	16 4	19 0	22 6	31 4	17 8	20 6	24 5	34 1			
H F	65 0	123	2 23	18 7	23 0	25 4	37 8	18 9	23 4	25 9	35 5			
Average			2 33	16 9	19 6	23 2	33 0	17 4	20 2	23 9	35 9			
M M T	66 0	108	2 32	15 7	18 7	21 5	29 8	18 8	22 5	25 9	35 9	More than 10 per cent under weight		
B W H	65 0	102	2 08	17 1	21 1	23 4	36 2	21 0	26 0	28 7	44 3			
V T	61 0	92	2 18	16 1	18 6	20 1	26 8	18 5	21 4	23 1	30 8			
F I	63 0	103	2 02	15 5	22 9	25 3	41 5	17 4	25 5	28 2	46 3			
E J	67 5	131	2 18	15 5	18 4	21 2	29 2	17 5	20 8	24 0	33 0			
Average			2 16	16 0	19 8	22 3	32 7	18 6	23 2	26 0	38 0			

during the test the ventilation should be proportional not to body surface or to body weight but to the mean between the two According to such a concept, the correct formula for calculation should be

$$\frac{\text{Distress (independent of nutritional state) due to exercise-ventilation per square meter}}{\text{vital capacity per square meter}} + \left[\frac{\text{ventilation per square meter}}{\text{vital capacity per square meter}} \times \frac{\text{ideal weight}}{\text{actual weight}} \right]$$

2

When this formula is simplified, it becomes

$$D_{\text{yspnea}} = \frac{\text{ventilation}}{\text{vital capacity}} \times \left[\frac{1 + \frac{\text{ideal weight}}{\text{actual weight}}}{2} \right]$$

Such an expression should be more or less independent of the nutritional state That this is actually the case is shown in table 8 The values

here are a mean between those in the right and left portions of table 7. It can be seen that both the individual and the average values lie closer together than in table 7. On the whole, the subjects whose weight is near the theoretical ideal have values slightly lower than the obese groups, the thin subjects being intermediate. This is illustrated in figure 2 in C.

Therefore, it seems that unless one is to have a series of different normal standards for subjects of varying degrees of nutrition, the method of calculation described is the best one to use in comparing

TABLE 8—The Ventilation Index in Subjects of Varying Nutritional States

Subject	Ventilation Index				Comment
	Exercise I	Exercise II	Exercise III	Exercise IV	
J W H	16.6	18.6	23.4	34.7	More than 10 per cent overweight
E C	18.1	19.4	23.3	41.9	
W G H	17.4	23.1	25.5	38.2	
C P C†	21.4	24.5	30.1	37.4	
G E C	17.3	19.7	23.7		
Average	18.1	21.1	25.1	38.2	
I A C	15.4	19.2	23.2	29.6	Within 10 per cent of ideal weight
T R H	16.4	17.9	21.9	31.2	
F C T	17.0	19.5	23.0	31.5	
J G M	18.3	20.0	23.9	37.6	
W J E	17.1	19.8	23.6	32.7	
H F	18.8	23.2	25.6	38.1	
Average	17.1	20.1	23.5	33.5	
M M T	17.7	20.6	23.7	32.8	More than 10 per cent underweight
B H	19.1	23.6	27.0	40.2	
V T	17.3	20.0	21.6	28.8	
F J	16.5	24.2	26.8	43.9	
E J	16.5	19.6	22.6	31.1	
Average	17.3	21.5	24.1	35.3	
Grand average	17.4	20.9	24.3	35.7	

$$* \text{ Ventilation index} = \frac{\text{Ventilation}}{\text{Vital capacity}} \times \left[1 + \frac{\text{Ideal weight} - \text{Actual weight}}{2} \right]$$

† This subject showed higher values than any other for three of the four points. Although there was no evidence of cardiac disease, both of his parents had it. The upper limits of normal are therefore considered to be 20, 23, 30, 40 for the respective exercises.

normal with pathologic subjects. It should be remembered, however, that the actual dyspnea is proportional to $\frac{\text{ventilation}}{\text{vital capacity}}$.

For the sake of brevity, the values as calculated in table 8 will be referred to as the ventilation index.

The Relation of the Ventilation Index to Sex and Age. As only 16 normal subjects were studied, sufficient data are not yet available to allow a statistical analysis. In table 9 are shown the highest, lowest and normal values for the two sexes. The average values for each exercise are a little higher for females, but the difference is not great. It is likely that studies of a larger number of cases would allow one to prepare separate standards for the two sexes. With the data at hand an attempt to do so seems unwarranted.

The influence of age is depicted in table 10 The data are too meager to draw final conclusions, but one can say that the ventilation index is at least relatively independent of age

TABLE 9—The Influence of Sex on the Ventilation Index of Normal Subjects

Number of Persons Studied		Ventilation Index				Sex
		Exercise I	Exercise II	Exercise III	Exercise IV	
10	{ Highest	21.4	24.5	30.1	38.2	Males
	{ Lowest	15.4	17.9	21.9	29.6	
	{ Average*	17.3	20.2	24.1	33.8	
6	{ Highest	19.1	24.2	27.0	43.9	Females
	{ Lowest	16.5	19.0	21.6	28.8	
	{ Average*	17.9	23.5	24.7	37.6	

* Mean of all the values, not of highest and lowest only

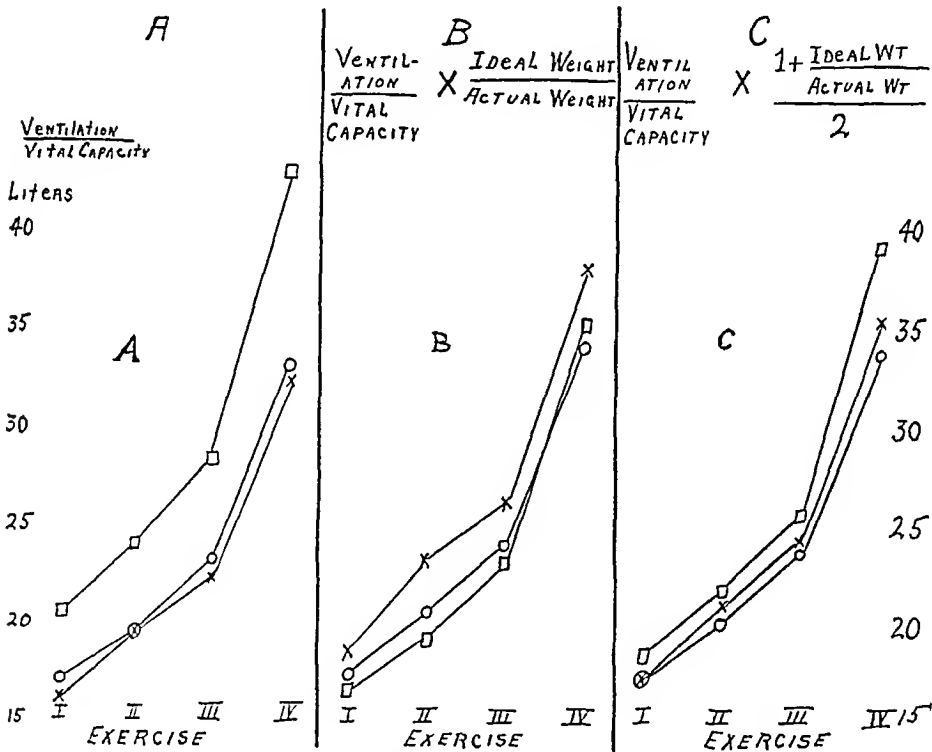


Fig 2—A shows values for $\frac{\text{ventilation}}{\text{vital capacity}}$ when no correction is made for body weight These values are seen to be considerably higher in the obese subjects and a little lower in the thin subjects than in the subjects of normal nutritional state B shows the values found when A is corrected by multiplying the results by the factor $\frac{\text{ideal weight}}{\text{actual weight}}$ The position for the curve is reversed, the obese group being lowest and the thin group highest It is evident that this correction factor is too large In C, the mean of the values obtained in A and B are plotted, the values for all of the subjects fall closer together, the normal group being lowest and the obese group highest It is evident that the method of correction for body weight used in C is preferable to that used in B The line with squares indicate the group of obese subjects, the line with the circles, the normal subjects, and the line with the x's, the thin subjects

Normal Standards for the Ventilation Index The normal standards are shown in table 8 The upper limits of normal for the various exercises can be considered as being approximately 20, 25, 30 and 40, respectively There are a few isolated values above these but no normal subject has a curve with every point above these levels

The average values for the four exercises are 17.4, 20.9, 24.3 and 35.7, respectively In normal subjects nine tenths of the values fall within

TABLE 10—*The Ventilation Index in Relation to Age*

Age Group	Number of Subjects	Average Ventilation Index			
		Exercise I	Exercise II	Exercise III	Exercise IV
Under 30	10	17.3	20.8	24.1	34.8
30 to 50	4	18.3	20.4	24.7	36.6
Over 50	2	17.3	21.2	24.5	35.4

15 per cent of these values, and all of such values fall within 20 per cent of them Therefore, any values that are more than 20 per cent above these averages are, in all probability, indications of a pathologic condition For practical purposes, it is simpler to regard any curve with three points above the line 20-25-30-40 as being abnormal For the sake of clarity a protocol illustrating the final method of calculation is given

SAMPLE PROTOCOL

Subject W. H., male, white, aged 59, July 2, 1930

Height, 67.5 inches Weight, 187 pounds Surface area, 1.98 square meters

Ideal weight, 151 pounds Weight factor $\left[1 + \frac{\frac{\text{Ideal weight}}{\text{Actual weight}}}{2} \right] = 0.90$

Diagnosis Normal

Temperature of spirometer, 27°C Barometer, 754 mm Hg

(1) Factor for temperature and barometer, 0.875

(2) Factor for spirometer, 1 cm = 1.59 liters

(3) Corrected factor for spirometer, (1) × (2) = 1.39

Vital capacity, 3.82 liters

Vital capacity per square meter, 1.93 liters

	Exercise I	Exercise II	Exercise III	Exercise IV
Spirometer difference	51.4 cm	69.9 cm	77.7 cm	115.8 cm
Total ventilation	71.5 liters	97.2 liters	107.9 liters	161.0 liters
Total ventilation per square meter	36.1 liters	49.1 liters	54.5 liters	81.3 liters
Ventilation	18.7 liters	25.4 liters	28.2 liters	42.1 liters
Vital capacity				

Ventilation index

$\frac{\text{Ventilation}}{\text{Vital capacity}} \times 1 + \frac{\frac{\text{Ideal weight}}{\text{Actual weight}}}{2}$ 16.8 liters 22.9 liters 25.4 liters 37.9 liters

The Ventilation Index in Patients with Various Diseases—The Ventilation Index in Subjects with Cardiac Neurosis Six persons were studied All of them had symptoms referable to the heart without

TABLE 11—*The Ventilation Index in Patients with Cardiac Neurosis*

Subject	Height, Inches	Weight, Pounds	Vital Capacity per Square Meter, Liters	Exercise I			Exercise II			Exercise III			Exercise IV			Comment
				Ventila- tion per Square Meter, Liters	Ventila- tion Index	Ventila- tion per Square Meter, Liters	Ventila- tion per Square Meter, Liters	Ventila- tion Index	Ventila- tion per Square Meter, Liters	Ventila- tion Index	Ventila- tion per Square Meter, Liters	Ventila- tion Index				
♀ R L M	66.0	121	1.92	31.8	17.2	42.0	22.7	47.5	25.7	70.6	38.0	Objective distress + with exercise IV sub- jective dyspnea ++ with exercise IV and + with III				
♀ L S	60.0	115	1.60	38.6	19.0	42.4	20.8	44.9	22.0	69.6	34.2	Objective distress + with exercise IV, sub- jective dyspnea + with all exercises				
♂ L U	73.5	138	2.88	41.2	16.7	45.1	18.2	48.3	19.6	77.2	37.6	Subjective and objective distress + with exercise IV				
♀ A L B	63.0	110	1.94	31.0	16.3	39.5	20.8	42.8	22.5	65.3	34.4	Subjective and objective distress + with exercise IV				
♀ A H	65.5	122	1.85	33.9	18.7	44.8	24.7	51.1	28.2	No objective distress, subjective distress + with I, ++ with II and III, refused to do exercise IV						
♀ F M	65.0	102	2.03	31.5	17.7	46.0	25.2	No objective distress, subjective dyspnea ++ with both exercises, refused to do exercises III and IV								

TABLE 12—*The Ventilation Index in Patients with Early Cardiac Disease*

Subject	Height, Inches	Weight, Pounds	Exercise I		Exercise II		Exercise III		Exercise IV		Dyspnea	Comment	
			Vital Capacity per Square Meter, Liters	Ventila- tion per Square Meter, Liters	Ventila- tion per Square Meter, Liters	Ventila- tion Index	Ventila- tion per Square Meter, Liters	Ventila- tion Index	Ventila- tion per Square Meter, Liters	Ventila- tion Index			
F B S	61.0	109	1.98	37.2	19.8	45.8	24.3	51.1	28.9	71.7	39.6	III + IV + IV +	Aortic insufficiency, ? rheu- matic, no cardiac enlargement Patent ductus arteriosus, no cardiac enlargement or symp- toms, swims, plays tennis
J H	64.0	130	1.93	40.7	20.3	49.3	24.6	59.8	29.8	87.0	43.3		Patent ductus arteriosus, no cardiac enlargement, no car- diac symptoms, athlete
A C	64.5	117	2.01	40.8	20.5	51.3	25.6			98.2	49.1	IV ++	Patent ductus arteriosus, no cardiac enlargement, no car- diac symptoms, athlete
D G C	67.5	126	2.34	51.5	24.2	57.7	27.2					II +	Hypertension, arteriosclerosis, slight cardiac hypertrophy, no cardiac symptoms
L C	78.0	130	1.60	41.2	34.5	58.1	45.5					I +	Hypertension, cardiac hyper- trophy
V B M	65.0	88	1.93	39.2	24.7	48.9	30.6	56.5	35.4	80.6	50.7	IV +	Hypertension, slight cardiac en- largement
H F	69.5	140	2.32	60.1	28.0	66.8	31.1	71.1	33.0	85.5	39.9	III + IV +	Rheumatic, myocarditis, no cardiac enlargement
V O V	61.0	141	1.40	41.2	25.3	49.1	30.1	*3.7	39.2			III +	Hypertension, slight cardiac hypertrophy
M L S	64.5	128	1.45	33.7	22.7	42.0	28.3	50.6	31.1	82.0	53.3	III + IV ++	Cardiac hypertrophy, cause un- known, paroxysmal auricular flutter
R O E	71.0	163	2.69	40.6	19.9	51.1	26.5					II +	Cardiac hypertrophy

demonstrable cardiac abnormality by physical, roentgenologic or electrocardiographic symptoms. Their vital capacities and their ventilation per square meter were within normal limits. For exercise I, their ventilation indexes were all below 20, and for exercise III and IV, were below 30 and 40, respectively. For exercise II, only 1 subject showed an index above 25.

Mention may be made of certain clinical features that were noted in connection with the tests in these subjects. The disproportion

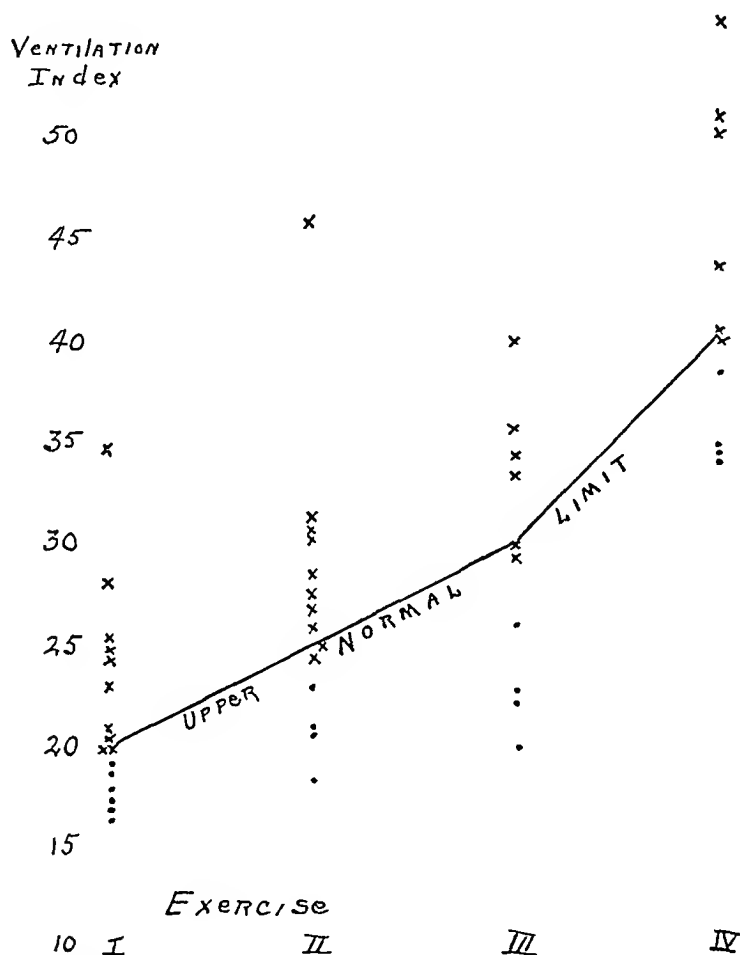


Fig 3—With very few exceptions the indexes for ventilation for the various exercises are at or above the upper normal limit in subjects with early cardiac disease (crosses) and at or below the upper normal limit in subjects with cardiac neurosis (dots)

between the apparent and the subjective distress was sometimes striking. However, we do not believe that these patients were malingering, but that they actually felt more dyspneic than did normal subjects under the same conditions. Another interesting feature is the fact that 2 of the 6 subjects refused to complete the test. No other patient has done this, even those with advanced cardiac disease have been willing to do

what they were asked to do, although subjects with cardiac decompensation have not, of course, been requested to perform any but the mildest exercises

The Ventilation Index in Subjects with Early Cardiac Disease Ten persons were studied. These patients had conditions representing various types of organic cardiac disease in the earliest stages in which a definite diagnosis could be made. Several of them had no cardiac symptoms, and several had no cardiac enlargement ascertainable by physical or by roentgen examination. None of them had ever had congestive failure. Their vital capacities were normal in 7 instances and reduced in 3. Their values for ventilation per square meter (table 12) were increased as compared with those of the normal subjects (table 2) in about half of the cases. The ventilation indexes were distributed as

TABLE 13—*The Ventilation Index in Subjects Who Had Previously Had Congestive Cardiac Failure*

Subject	Height, Inches	Weight, Pounds	Vital Capacity per Square Meter, Liters	Exercise I		Ventila- tion Index	Comment
				Ventila- tion per Square Meter, Liters	Dyspnea		
R B	65.5	105	1.74	49.3	+	32.9	Syphilitic aortic insufficiency, one "break"
E G	66.0	118	1.57	49.2	+	34.4	Syphilitic aortic insufficiency, three "breaks"
W C	70.5	148	1.82	62.0	±	36.3	Hypertension, four "breaks"
W S	67.5	135	1.85	40.6	0	22.5	Hypertension, one "break"
T R	70.0	133	2.64	80.6	+	33.5	Hypertension, aortic insufficiency, four "breaks"
J A	66.0	118	1.78	60.2	0	37.3	Auricular fibrillation, four "breaks"

follows: (a) just below the upper normal limit, 1 case, (b) at the upper normal limit, 1 case, (c) above the upper normal limit, 8 cases. From these data it seems clear that the great majority of patients with even very early cardiac disease have an increased ventilation index.

In figure 3 the ventilation indexes of these patients are compared with those of persons with cardiac neurosis. The difference is striking. A few borderline values were obtained, but this is to be expected when one is dealing with disease in very early stages.

The Ventilation Index in Subjects with Congestive Cardiac Failure In table 13 are shown observations in 6 cases in which there had previously been decompensation, but in which there was compensation when the test was performed. For exercise I, 5 of the 6 subjects had values above 30 for the ventilation index (average normal, 17.4, upper normal limit, 20). The sixth subject had a value only slightly above normal. He had had only one "break" in compensation, most of the others had had several "breaks."

The results in subjects with congestive cardiac failure at the time of the test are shown in table 14. The vital capacity was decreased, and the ventilation per square meter was increased in every instance. The ventilation indexes were greatly increased. A comparison of tables 13 and 14 indicates that the ventilation index is a more accurate measure of the patient's state than is the vital capacity. Four subjects (T R, J A, W C and W S) are listed in both tables. In each of them the ventilation index changed more with the restoration of compensation than did the vital capacity.

The prognostic value of the ventilation index is shown in figure 4. In the patient who improved, the ventilation index steadily decreased, whereas, a rising ventilation index occurred in the subject who died. Changes in body weight and in vital capacity are also plotted. In these

TABLE 14—*The Ventilation Index in Subjects with Congestive Heart Failure*

Subject	Height, Inches	Weight, Pounds	Vital Capacity per Square Meter, Liters	Exercise I		Ventila- tion Index	Comment
				Ventila- tion per Square Meter Liters	Dyspnea		
T R	70.0	144	1.94	85.2	+++	47.3	Hypertension, aortic insufficiency
J A	66.0	131	1.48	89.6	+++	53.0	Auricular fibrillation
S W	60.0	233	1.07	55.4	++	37.3	Hypertension, aortic insufficiency
S P	64.0	151	1.48	52.0	++	35.1	Hypertension
M G	62.0	180	1.15	60.7	++	52.8	Hypertension
W C	70.5	168	1.44	72.4	++	49.8	Hypertension
W S	67.5	147	1.62	47.6	+	29.7	Hypertension
J U	69.0	130	1.20	60.7	+++	50.6	Hypertension, emphysema
P C	66.0	127	1.60	70.6	++	46.4	Rheumatic, aortic and mitral endocarditis

subjects the vital capacity was of no prognostic value. The body weight paralleled the ventilation index in one subject, but not in the other.

(In patients with cardiac insufficiency only the data for exercise I have been presented. In most of the instances this was the only exercise performed because the patient was too short of breath to do more. However, a number of these patients performed exercise II as well. As the results are entirely in accord with those obtained from exercise I, being at a corresponding but higher level, they are not presented. Patients with moderately or far advanced cardiac disease were never requested to perform exercise III and IV.)

The Effect of Respiratory Obstruction. Experiments have been carried out on normal subjects under a number of different conditions and on patients with various diseases, and the general principle that $\frac{\text{ventilation}}{\text{vital capacity}} = \text{degree of dyspnea}$ has seemed to hold true in all instances except in subjects with respiratory obstruction (patients with cardiac neurosis are also an exception if one accepts their statement as to dyspnea, but not if the objective evidences are relied on).

Respiratory obstruction was produced in two normal subjects by inserting coiks with holes of 4 mm in diameter into the inspiratory and expiratory valves. As can be seen from table 6, these subjects suffered from considerably more than their usual respiratory distress in performing the various exercises. Although the dyspnea was greater, all the values for ventilation per square meter and for $\frac{\text{ventilation}}{\text{vital capacity}}$ were lower than when these subjects performed the same exercises under normal conditions. Therefore, it is evident that respiratory measure-

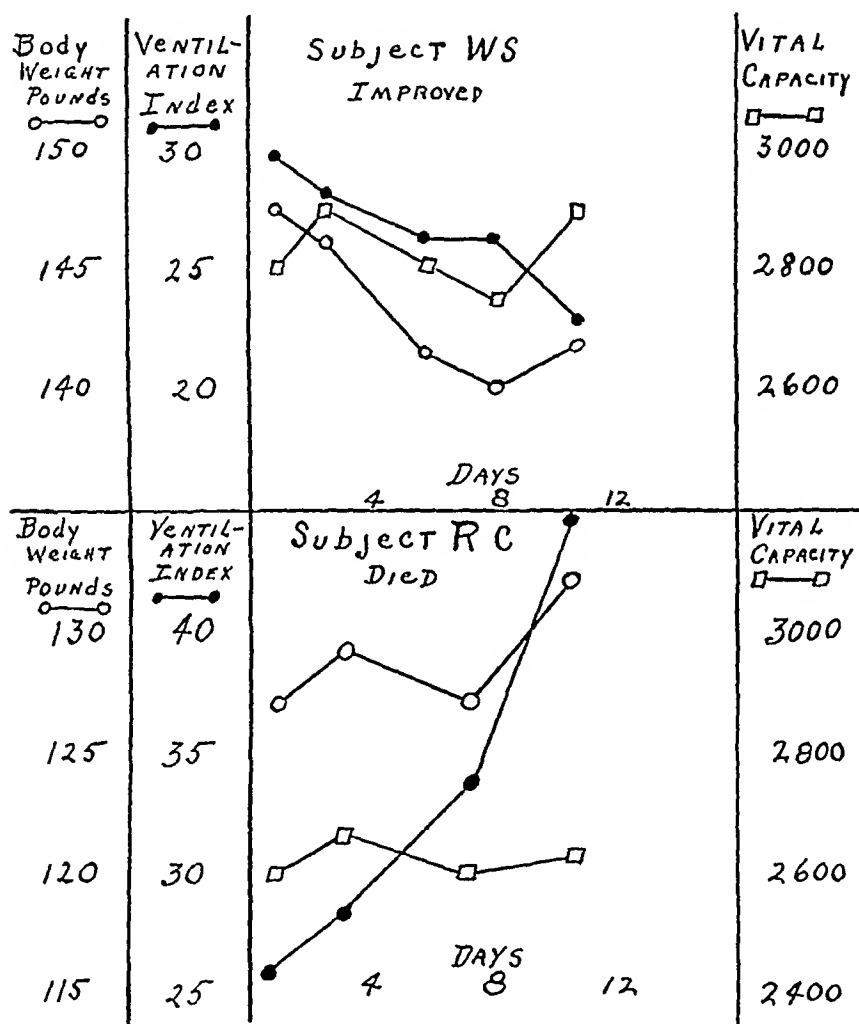


Fig 4—Ventilation index in two subjects. In neither subject was there a striking change in the vital capacity. Improvement was associated with loss of weight and diuresis in W S, but there was no constant tendency for R C to gain weight as he became worse. In both subjects the change in weight was relatively slight. The direction of the change of the ventilation index was a reliable prognostic guide in both cases.

ments such as those we have carried out furnish a misleading index to the degree of dyspnea in subjects with respiratory obstruction.

The Ventilation Index in Subjects with Hyperthyroidism and in Subjects with Anemia. As can be seen from table 15, patients with

TABLE 15—*The Ventilation Index in Patients with Hyperthyroidism and in Patients with Anemia*

Subject	Height, Inches	Weight, Pounds	Exercise I				Exercise II				Exercise III				Exercise IV			
			Vital Capacity		Ventilation		Ventilation per Square Meter,		Ventilation per Square Meter,		Ventilation per Square Meter,		Ventilation per Square Meter,		Ventilation per Square Meter,		Ventilation per Square Meter,	
			Liters	Liters	Dyspnea	Index	Liters	Liters	Dyspnea	Index	Liters	Liters	Dyspnea	Index	Liters	Liters	Dyspnea	Index
A P	64.0	123	1.72	40.5	0	25.2	78.3	+	48.8	53.2	93.4	++	53.2					
A H	66.0	113	1.58	36.2	0	24.6	46.7	0	31.8	35.2	51.7	+	35.2		71.0	++	48.3	
D A	68.0	112	2.11	43.8	0	21.1	58.2	+	23.5									
R L K	61.0	93	1.80	47.3	0	28.0	51.1	0	30.2	33.5	56.8	+	33.5					
R A	65.0	105	1.99	40.8	0	22.4	45.1	0	24.7	30.1	56.6	+	30.1		72.5	+	39.9	

Hyperthyroidism,
basal metabolic
rate + 50

Hyperthyroidism,
basal metabolic
rate + 35

Secondary anemia
hemoglobin 10

Secondary anemia,
hemoglobin 50

Secondary anemia,
hemoglobin 52

hyperthyroidism and anemia showed values somewhat above the normal. This was to be expected in hyperthyroidism as this disease when of severe degree may be considered as being always associated with early cardiac disease. The patients with anemia showed hemoglobin values of 50 or below. No cases of mild anemia were studied. Although, according to Cabot,⁴ severe anemia may be associated with cardiac enlargement, none of our 3 cases showed evidence of this. It seems likely that severe anemia per se causes an increase in the ventilation index. If the test is to be used to detect cardiac disease, it is evident that one must first be certain that the patient is not anemic.

COMMENT

From the data that have been presented, it seems clear that when there is no obstruction to breathing, subjective respiratory distress (dyspnea) on exertion is dependent on three factors. These are (1) the volume of the ventilation, (2) the vital capacity, and (3) the sensitiveness of the psyche. The third factor is unimportant except in neurotic persons. It is evident that, as Peabody pointed out, one feels short of breath when his breathing is greater than a certain fraction of his maximum ventilation.

The actual dyspnea is dependent not only on the presence or absence of disease of the various organs concerned in internal and external respiration, but also on the nutritional status. By means of appropriate correction, however, it is possible to eliminate more or less from consideration differences in nutrition and to obtain figures which are somewhat proportional to the degree of functional alteration of the heart or other portions of the respiratory-circulatory apparatus. However, it should be noted that the actual distress and the actual respiratory measurements were the same in obese persons with normal hearts as in subjects with early cardiac disease and normal nutritional status. This fact indicates the great importance of reducing the weight of obese patients with cardiac conditions.

We believe that the ventilation index affords a fairly accurate objective answer to the question "How short of breath are you?" For this reason it seems a better guide to cardiac function than other tests that have been devised. It seems probable that the test will be of some value in measuring the effect of various therapeutic measures, such as the administration of digitalis, in patients with different types of cardiac disease in various stages of development.

The question arises as to whether, aside from research, the measure is of practical value. Our experience with the test is not yet sufficiently

⁴ Cabot, Richard C. *Facts on the Heart*, Philadelphia, W. B. Saunders Company, 1926, p. 470.

broad to allow any certain answer to this question. The observations that have been reported for patients with cardiac neurosis and for those with very early cardiac disease suggest that the method may be of some diagnostic as well as prognostic value. Studies along this line are in progress.

SUMMARY

1 A series of standard exercises has been described during and after which the ventilation was measured.

2 Dyspnea is directly (but only roughly) proportional to the ventilation per square meter.

3 Dyspnea is inversely proportional to vital capacity, but again the agreement is rough.

4 The degree of dyspnea is fairly closely proportional to the expression $\frac{\text{ventilation}}{\text{vital capacity}}$.

5 The actual dyspnea is greater in obese subjects and often less in very thin subjects than in persons of normal nutritional status. The

expression $\frac{\text{ventilation}}{\text{vital capacity}} \times \left[\frac{1 + \frac{\text{ideal weight}}{\text{actual weight}}}{2} \right]$ has been denoted as the ventilation index and the values for this are relatively independent of the nutritional state.

6 The ventilation index is usually normal in subjects with cardiac neurosis.

7 The ventilation index is usually slightly above normal in subjects with early organic cardiac disease, and is very much above normal in patients who have or who have had congestive failure.

8 The ventilation index is also increased in persons with diminished vital capacities from pulmonary disease, in subjects with hyperthyroidism and in patients with severe anemia.

9 The test is useless and actually misleading in persons with respiratory obstruction.

THE STAFF COUNT

ITS IMPORTANCE IN ACUTE INFECTIOUS DISEASE³

ARTHUR WEISS, M D

NEW YORK

The publications of Arneth in 1904 came as the result of the impetus given to the study of hematology by the introduction of Ehrlich's blood stains. Up to his time morphologic studies had been more or less limited to hematologic conditions. While studying the nuclear structure of the neutrophils in infection, Arneth¹ found that there seemed to be a constant relationship between the severity of the infection and the number of nonsegmented neutrophils. If the infection was very severe, neutrophils with three, four or five-lobed nuclei would disappear, to be replaced by others with nonsegmented nuclei. With the abatement of the infection, the nonsegmented neutrophils would rapidly be replaced by the mature forms. His later observations on the other leukocytes, though painstaking and correct, never received confirmation. Even his neutrophilic subclasses, though widely employed over an extended period of time, were never universally adopted. Schilling,² finding this classification cumbersome and impracticable, offered the same information in a simplified and more practicable formula. Instead of the numerous subclasses of neutrophils that depended on the shape and number of nuclear segments, he combined all of the segmented forms into one group called the segmented, and all of the nonsegmented into "jungkernige" and "stabkernige". The "stabkernige" form was an immature neutrophil, the nucleus of which, though nonsegmented, was thin and assumed many forms. The "jungkernige" form, however, usually was sausage-shaped and showed no indication of oncoming segmentation. Furthermore, instead of separately classifying 100 neutrophils, he included them in the differential count.

Since the appearance of my preliminary report in 1927³ on the newer hematologic aspects of the neutrophils in infection, the study of the morphologic structure of the leukocytes has been continued. During the past five years, about 20,000 blood smears taken from patients with

³ Submitted for publication, Dec 3, 1930

^{*} From the Hematological Laboratory of Beth Israel Hospital

1 Arneth, cited by Klinkhardt. *Qualitative Leukocytose*, 1920, vol 1, p 2

2 Schilling, V. *Das Blutbild und seine klinische Verwertung*, ed 4, Jena, Gustav Fischer, 1924, vol 3, *Biologische Leukocytenkurven*, *Deutsche med Wchnschr* 50 1583, 1924

3 Weiss, Arthur. *Am J M Sc* 174 45 (July) 1927

a large variety of medical and surgical infections were examined. Complete examinations of the blood were carried out daily in most cases. When deemed necessary, examinations were made even more frequently. These blood counts were usually taken between 9 and 11 a. m., and were timed so that tests were usually obtained from the same patient at the same time. Blood films were stained according to the Jenner-Giemsa method, and a differential count of 200 or 300 cells was usually performed.

The following cases demonstrate the employment of this formula

REPORT OF CASES

CASE 1—G. S., a woman, aged 21, was admitted to the medical service of Beth Israel Hospital on Jan. 10, 1929, complaining of cough, fever and pain in the right side of the chest. She had gone to bed complaining of lassitude and slight headache, and was aroused from a deep slumber because of a sudden, sharp, lancinating pain in the right side of the chest. She found that she had fever, and that she breathed with difficulty.

On physical examination, the patient appeared to be acutely ill. Examination gave negative results except for local signs in the chest. There were fine, moist, intrapulmonary râles and pleural friction sounds. There was a diminished and distant respiratory murmur over the right side of the chest anteriorly. Breathing was bronchovesicular. Four days later, tubular breathing was elicited over the right side of the chest, anteriorly and posteriorly. The heart sounds were regular, although somewhat distant. On admission, the temperature was 105.4 F., the pulse rate, 128, and the respiratory rate, 30. During the patient's illness, the pulse rate rose to 150. She was critically ill and toxic for one week, and the prognosis seemed poor.

Urinalysis revealed a specific gravity of from 1.010 to 1.036, a trace of albumin and a few white blood cells. A roentgenogram of the chest showed consolidation at the base of the left lung; there was compensatory emphysema of the left lung.

This patient had lobar pneumonia and clinically was very toxic. As the toxicity started early in the disease and increased as the disease progressed, the prognosis seemed extremely poor. From table 1 it can be seen that whereas the white blood cells were but slightly increased, the percentage of neutrophils, especially that of the staff cells, was high (70 per cent). In spite of the extreme toxicity, repeated examinations of the blood soon showed, by means of a gradual drop in the percentage of staff cells, that the patient would recover. Figure 1 shows the parallel rise and descent of the curves for the neutrophils and the staff cells. Another point of significance can be noted by examining the counts of January 11, 14 and 15. The total leukocyte count on these three days is of but slight significance. Although January 11 was the day preceding the high level of the staff count and January 15 the day showing a marked decrease in the staff count, all three days showed a neutrophil count above 90 per cent. If, therefore, one were to judge by the leukocyte and neutrophil counts, one would miss the evident action of the immature cells.

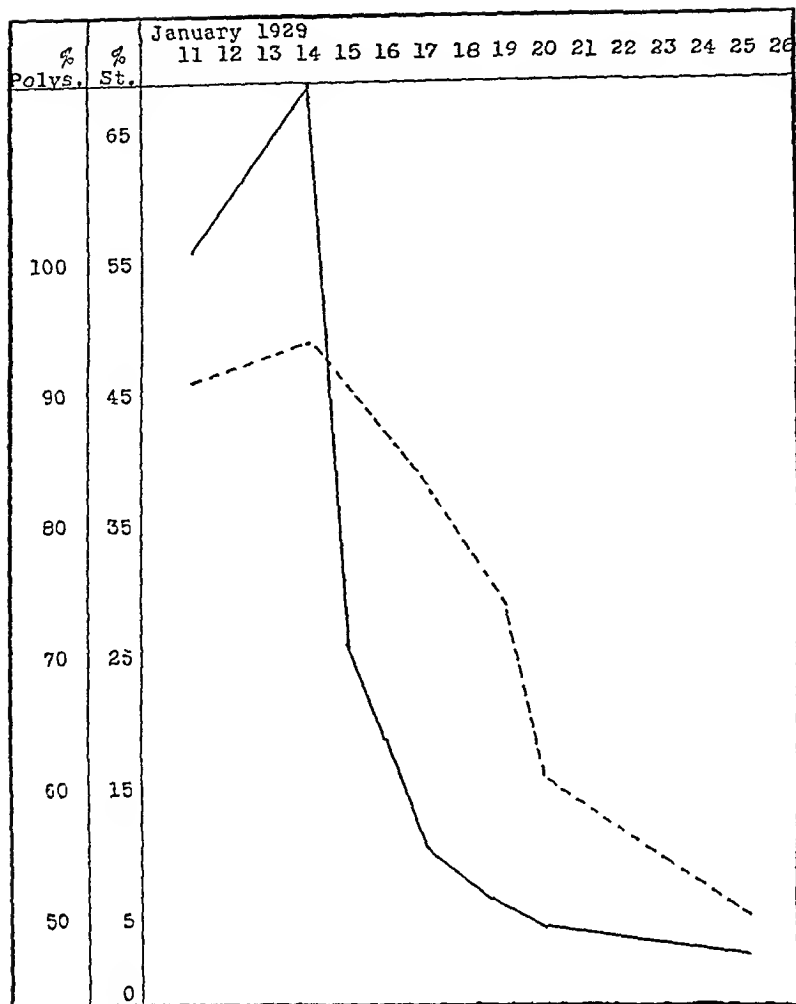


Fig 1 (case 1) —Graph showing a sharp rise in the staff count before, and a decisive fall and return to normal after, the crisis. The percentage of polymorphonuclear neutrophils shows a similar though slower reaction.

TABLE 1—Results of Examinations of the Blood in Case 1

Date, 1929	Erythrocytes, No in O Mm	Hemoglobin, per Cent	Leukocytes, No in O Mm	Total per Cent		Polymorphonuclear				Mono- nuclear		Comment
				Polymorpho- nuclears	Mononuclears	Metamyelocytes	Staff Cells*	Segmented Neutrophils	Basophils	Eosinophils	Segmented Monocytes	
1/11	4,500,000	80	15,200	92	8		57	35		8		
1/14	4,000,000	65	10,200	95	5		70	25		5		
1/15			16,200	91	9		27	64		8	1	Marked degeneration of neutrophils
1/16			18,600	89	11		21	68		8	3	
1/17			18,200	86	14	2	12	74		4	8	
1/18			21,000	75	25		9	66		17	8	
1/20			14,500	62	38		6	53		3	2	
1/25			11,200	53	47		3	47		1	4	

* There was severe stimulation of the bone marrow, the staff cells rising as high as 70 per cent at the crisis. The number of leukocytes and the percentage of polymorphonuclears are of relatively minor importance.

CASE 2—I S, a man, aged 41, was admitted to the hospital on Nov 25, 1929, with the complaint of fever. He had been operated on for acute appendicitis on October 27. At that time general peritonitis and bronchopneumonia had developed. After a stormy course, his temperature had dropped, the wound had closed, and he had been discharged from the hospital as cured. During his first night at home his temperature rose to such a degree that a physician who was called advised his immediate return to the hospital. Thus, a week after his discharge he was readmitted, appearing pale but not otherwise ill. The abdominal wound was not completely healed, but in spite of tenderness over the area of the wound, it did not show abnormality. There were diminished resonance and voice sounds, with distant breath sounds over the lower lobe of the right lung below the level of the eighth rib. Above this level there was a small area throughout which the voice sounds were somewhat louder than normal. On admission, the temperature was 102.6 F, and during his stay in the hospital it rose as high as 104 F. A roentgenogram of the chest taken on November 26 showed mild congestion of both lungs, with interstitial changes in the base of the right lung, productive changes

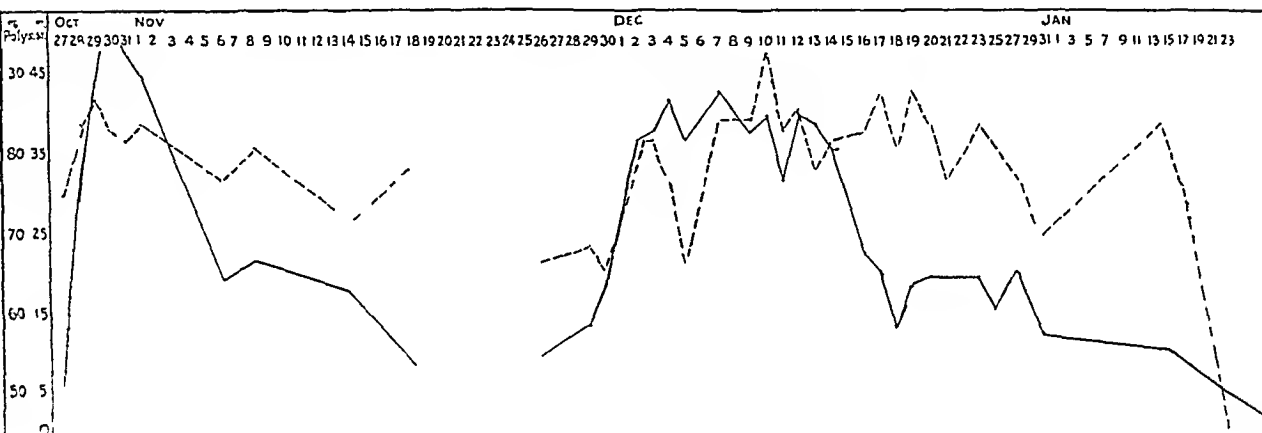


Fig 2 (case 2)—Graph showing a precipitate rise in the staff count immediately after operation. The peak of the rise (54 per cent) was reached three days after operation, the count dropped to 9 per cent on the day of discharge. On readmission, there was a rapid rise in the immature cell count (43 per cent) within eleven days. The level remained high for one week and then gradually returned to normal.

at the roots of both lungs and generalized enlargement of the cardiac shadow. Repeated aspirations of the right side of the chest yielded some broken-down tissue and a small amount of fluid, examination of which showed streptococci. On December 6, a costal resection was performed and a subphrenic abscess was found. The abscess was drained, and 3 ounces of pus were evacuated. On December 18, thoracotomy was performed for empyema, and 30 ounces of fluid were evacuated. A smear of the thoracic fluid showed streptococci in long chains. Cultures of the blood repeatedly gave negative results.

Table 2 demonstrates that examination of the blood showed a slight reaction of the bone marrow. The examination performed the day after operation, however, showed a marked increase in the staff cells. The patient's postoperative course was extremely turbulent, the imma-

ture cells rising as high as 54 per cent. There was a concomitant decrease in the hemoglobin and the erythrocytes. The neutrophils showed marked toxic degeneration. Twenty-two days after appendec-

TABLE 2—Results of Examinations of the Blood in Case 2

Date, 1923	Erythrocytes, No in C Mm	Hemoglobin, per Cent	Leukocytes, No in C Mm	Total per Cent		Metamyelocytes	Polymorphonuclear			Mono nuclear		Comment	
				Polymorpho nuclears	Mononuclears		Staff Cells	Segmented Neutrophils	Basophils	Eosinophils	Segmented		Monocytes
10/27	5,150,000	80	10,400	75	25		5	70			18	7	
10/28			16,000	84	16		30	54			12	4	
10/29			18,200	88	12	1	42	45			8	4	
10/30			12,000	83	17		54	29			15	2	Toxic degeneration of leukocytes
10/31			13,000	82	18		48	34			14	4	Toxic degeneration of leukocytes
11/ 1			13,000	84	16		45	37		2	16		Toxic degeneration of leukocytes
11/ 6	4,530,000	68	11,400	77	23	1	20	56			19	4	
11/ 8			13,200	81	19	1	21	59		1	16	2	
11/14			9,000	72	28	1	17	54			25	3	
11/18	4,500,000	68	7,800	78	22		9	59			20	2	Discharged Readmitted
11/25													
11/26	4,420,000	64	8,600	67	33	3	7	55	1	1	31	2	
11/29	4,390,000	69	9,400	69	31	2	12	55			28	3	
11/30	4,420,000	68	16,200	66	34	2	17	47			31	3	
12/ 2			13,600	82	18	2	30	50			13	5	
12/ 3	3,860,000	68	9,000	82	18	3	34	44			15	3	One myelocyte
12/ 4			8,200	77	23	5	37	35			19	3	One myelocyte
12/ 5			12,000	67	33	5	32	30			29	4	Costal resection
12/ 7			14,400	85	15	2	41	41		1	9	6	Toxic degeneration of leukocytes
12/ 9			18,000	85	15	4	34	46			12	3	One myelocyte
12/10			22,800	93	7	2	38	53			5	2	Toxic leukocytes, anisocytosis
12/11			19,600	83	17	2	30	50		1	13	4	Toxic leukocytes
12/12			16,400	85	15	2	38	45			10	5	Toxic leukocytes
12/13			18,600	78	22	1	38	39			14	8	Platelets increased, slight macrocytosis
12/14	4,270,000	63	17,200	82	18	1	35	46			14	4	Platelets increased, slight macrocytosis
12/16	3,780,000	62	15,000	83	17	1	22	60			13	4	Anisocytosis, slight polychromatophilia
12/17			12,400	88	12	1	20	66	1		8	4	
12/18			10,800	81	19		14	67			14	5	Thoracotomy
12/19			17,000	88	12	1	17	68			10	4	Platelets increased
12/20	3,300,000	57	13,800	84	16	1	18	65			12	4	Anisocytosis
12/21			13,000	77	23	1	18	58			14	9	Polychromatophilia
12/23			12,800	84	16	1	18	65			12	4	
12/24			11,000	82	18		16	63	1	2	12	6	Platelets increased
12/28	3,410,000	63	10,000	77	23	3	17	55	1	1	20	3	
12/30	3,700,000	65	8,400	69	31		13	55			24	7	One myelocyte
1930													
1/15	3,780,000	69	16,400	84	16		11	72		1	11	5	
1/16			16,200	76	24	1	9	64		1	22	2	
1/23			7,800	46	54		6	38		2	50	4	One myelocyte

* The blood picture was normal except for a slight leukocytosis, which became much worse the day after appendectomy. The staff count held its high level until shortly before the patient's discharge. Immediately after readmission, however, the staff count started to rise and increased even after costal resection. At the time of the thoracotomy for empyema, the level of the staff cells had already started to descend.

tomy, the patient was discharged as apparently cured. Eight days later he was readmitted. The chart shows a gradual but progressive increase in the immature neutrophils during the first week after the second admission. Costal resection, which was performed on December 6, revealed

a subphrenic abscess Examination of the blood on the following day showed a marked increase in the immature cells Twelve days later thoracotomy was performed, and 30 ounces of pus was removed At this time the blood picture showed a slow but progressive decrease in the immature neutrophils Thirty-seven days after the thoracotomy, an examination of the blood showed a normal leukocyte count, a normal staff count and an increase in the lymphocytes Figure 2 shows a precipitate rise in the staff cells and a gradual return to normal, with recovery The second part of the graph shows the rapid rise and the sustained level of the staff cells for a period of three weeks Costal resection apparently had no influence on the curve Whereas the percentage of neutrophils was irregular and high, the staff count began its return to normal even before there were any signs of clinical improvement

CASE 3—I M, a woman, aged 38, was admitted to the medical service of Beth Israel Hospital on April 22, 1930, with a condition diagnosed as acute diverticulitis Her chief complaints were severe abdominal cramps, weakness, anorexia and dryness of the mouth and lips Four days before admission, following her usual supper, the patient felt slight epigastric pain, to which she paid little attention The continuation of this pain caused her to sleep poorly In the morning, shortly after arising, she was seized with moderately severe abdominal cramps, and therefore did not eat breakfast or luncheon In the afternoon she attended a clinic to have an infected finger dressed On her way home, she was seized with an attack of severe, generalized, abdominal cramps, and barely managed to reach her home She vomited soon afterward and had considerable gaseous eructation The cramps continued irregularly for the next three days Slight relief was obtained from an enema, which yielded a moderate fecal return There were nausea, retching and gaseous eructation During this time, the patient was under medical care and received a great deal of medication She had had no bowel movements for three days before the onset of the illness At no time had the patient noticed blood in the stools, she gave no history of chills, jaundice or melena Because of the increasing weakness and anorexia, hospitalization was considered imperative For many years the patient's diet had consisted mainly of vegetables and dairy foods The bowels had always been sluggish, and purgatives had frequently been necessary

Physical examination revealed the patient to be poorly nourished, anemic, sunken-eyed and dehydrated, she was lying in bed, moaning, and appeared acutely ill Examination of the chest showed some dullness, with diminished breath and voice sounds over the base of the right lung in the axillary region The abdomen was rounded and somewhat distended Palpation revealed a slight generalized rigidity, which was probably a little more marked in the right upper quadrant There was also generalized tenderness In the right upper quadrant of the abdomen there was a resistance suggestive of an indefinite mass The abdominal reflexes were not elicited There was an infection of the distal end of the second finger of the left hand A roentgenogram of the chest did not show consolidation or infiltration of either lung, pleural changes or deviation of the mediastinal contents On admission, the temperature was 101.6 F, the pulse rate, 112, and the respiratory rate, 30 During the week that the patient remained in the hospital, the temperature gradually rose to 104.5 F, the pulse rate to 150 and the respiratory

rate to 56 The urine showed albumin, a few granular casts, a moderate number of white blood cells and a few red blood cells Cultures of the blood were repeatedly negative, the sedimentation rate was repeatedly as high as 68 per cent

Table 3 shows that there were a moderate anemia and a marked increase in the number of leukocytes, with a marked increase in the neutrophils and staff cells There was a concomitant decrease in the lymphocytes and monocytes Perusal of figure 3 also shows that there was a sustained high level of the neutrophils and staff cells

Repeated surgical consultations were invited, but the surgeons did not believe that a definite lesion of any abdominal viscera could be found They therefore were of the opinion that the condition did not call for surgical intervention The medical men, however, taking into

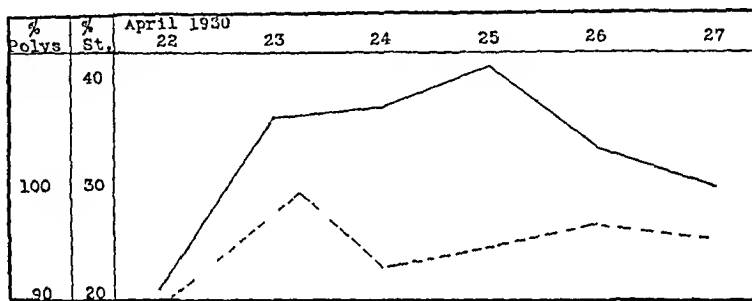


Fig 3 (case 3) —Graph showing the curve of the staff cells and polymorphonuclears, there was no tendency to return from their elevated level to normal

TABLE 3—Results of Examinations of the Blood in Case 3

Date, 1930	Erythrocytes, No in C Mm	Hemoglobin, per Cent	Leukocytes, No in C Mm	Total per Cent		Polymorphonuclear				Mono nuclear		Comment	
				Polymorpha nuclears	Mononuclears	Metamyelocytes	Staff Cells	Segmented Neutrophils	Basophils	Eosinophils	Segmented		Monocytes
4/22			25,500	90	10		21	69			8	2	
4/23	3,920,000	72	17,600	98	2	2	34	62			1	1	
4/24	3,600,000	71	15,800	93	7		33	55			6	1	
4/25	3,420,000	71	20,800	95	5	2	40	53			4	1	
4/26			21,500	97	3	2	32	62			3		
4/28	3,470,000	70	28,600	94	6	1	30	61			5	1	One myelocyte Two myelocytes, toxic degeneration of neutrophils

* In addition to a high leukocyte and polymorphonuclear neutrophil count, there was a high and progressively increasing staff count

consideration the patient's history, the physical findings of a suggestive mass in the right upper quadrant of the abdomen, the laboratory observations of an exceedingly high rate of sedimentation and repeated examinations of the blood indicating pus, were of the opinion that a condi-

tion requiring surgical attention was present in the environs of the liver. The patient died, and a subhepatic abscess was found post mortem. In this case, the presence of a high staff count, which showed no tendency to decrease to normal, and the presence of physical signs pointing to disease in the right upper quadrant of the abdomen, should, I believe, have been sufficient to warrant operative intervention.

CASE 4—C S a man, aged 50, was admitted to the hospital on Dec 13 1929. On admission, his chief complaint was pain in the left lower quadrant of the abdomen of twelve days' duration. Twelve days prior to admission, he had had a sudden attack of sharp, shooting pain in this region, occasionally radiating across to the opposite side of the abdomen. The pain was not related to the ingestion of food, exertion or posture. Accompanying these attacks of pain, his temperature had risen to between 101 and 103 F. During this period, the patient had had few intervals that were free from pain. During the attacks of pain, the abdomen had become swollen in the lower quadrant and tender to touch. After several days he had had slight pain on defecation. After proctoscopy the patient had passed a bloody stool. Pain in the left lower quadrant of the abdomen had persisted unabated. Eight days before admission, following an enema, the patient went into collapse. He had marked weakness, a rapid pulse, marked dyspnea and pallor. There was a history suggestive of a similar attack almost a year before admission, which stopped spontaneously after three or four days.

On physical examination, the patient was found to be well developed and moderately obese, he complained of pain in the left lower quadrant of the abdomen. He did not look acutely or chronically ill. The temperature was 99 F, the pulse rate, 92, and the respiratory rate, 22, the blood pressure was 116 systolic and 80 diastolic. Examination of the chest gave negative results. There was a marked bulge in the lower part of the abdomen, particularly toward the left, with marked tenderness and slight rigidity over the entire abdomen. There was a large, palpable mass, mainly to the left of the midline, extending from 5 cm above the umbilicus almost to the symphysis. Genito-urinary examination gave negative results. A roentgenogram of the colon showed no obstruction to the inflow of barium; the column passed rapidly to the cecum. There was spasticity of the sigmoid and the descending colon, with intermittent filling.

Urinalysis revealed a specific gravity of 1.024, acetone of 3+, a few red blood cells, occasional white blood cells and occasional hyaline and finely granular casts. The rate of sedimentation was 15 per cent. Examinations of the blood on December 13 and 14 showed, respectively: red blood cells, — and 5,310, hemoglobin, — and 91, white cells, 65,000 and 66,200, metamyelocytes, 6 and 5, staff cells, 25 and 31, segmented neutrophils, 57 and 53, basophils, 1 and 2, eosinophils, 0 and 4, lymphocytes, 2 and 4, monocytes, 1 and —, and myelocytes, 8 and 4. Toxic degeneration of the neutrophils was noticed at the first examination and marked anisocytosis at the second. The patient was operated on on December 14, and a large perisigmoid abscess was found. The sigmoid and small intestines were matted together and adherent to the peritoneum.

This case is of interest because it demonstrates that the blood picture is far more reliable in indicating the condition of a patient than his appearance. When I visited this patient before the operation, he sat in bed smoking a cigar, being barely inconvenienced by pain. No one who saw this man so comfortable and apparently healthy could have

believed that he would die on the following day because of a pathologic process that he was harboring at that moment. However, an examination of the blood revealed the extreme seriousness of his condition.

CASE 5—H. K., a woman, aged 61, was admitted to the ward at Beth Israel Hospital with a condition diagnosed as cholecystitis and cholelithiasis. Her chief complaints were abdominal pain and vomiting. The onset of symptoms had been sudden, with sharp, excruciating pain in the right upper quadrant, which radiated to the back. A few hours later she vomited some greenish fluid. A physician who was called in found the patient's temperature to be 101.2 F, and he prescribed medication to relieve the fever and pain. Three days later, on the day prior to admission, the patient experienced another attack. The temperature rose to 102 F, and hospitalization was advised. Fourteen years before, the patient had had "gallbladder trouble." She had had her last attack eleven years before. Although she had had no definite attacks since, she was never absolutely symptom-free. Her regimen had consisted of a lactovegetarian diet and of Carlsbad salts taken daily. She had never been jaundiced.

Physical examination revealed the patient to be acutely ill. The skin was moist and slightly icteric. There were a few scattered râles at the base of both lungs. Abdominal examination showed generalized tenderness, which was most marked in the right upper quadrant. Rigidity and tenderness of the right upper quadrant apparently covered a mass that seemed to extend to the umbilicus. On admission, the temperature was 104 F, the pulse rate, 112, and the respiratory rate, 24. The blood pressure was 105 systolic and 70 diastolic. A roentgenogram of the chest showed the right side of the diaphragm to be elevated though freely movable. The urine contained albumin, 4+, and many white blood cells and granular casts; it was positive for bile. Surgical consultation was requested on the day of admission and the consultant advised observation.

Examination of the blood revealed red cells, 4,340,000, hemoglobin, 80, white cells, 13,000, metamyelocytes, 6, staff cells, 27, segmented neutrophils, 47, lymphocytes, 14, and monocytes, 6; there was marked degeneration of the neutrophils.

Operation performed on the following day disclosed a large amount of bile in the peritoneal cavity and a ruptured gallbladder, with a stone in the gallbladder and in the cystic duct. With the blood picture showing 33 per cent of neutrophils, the patient should have received surgical care immediately.

COMMENT

What is the morphologic condition of the blood in acute infections, and what is revealed by a careful inspection of that mirror of physiologic and pathologic processes? Years ago it was taught that every infection resulted in leukocytosis and an increase in the polymorphonuclear leukocytes. To this was added the corollary that the higher the number of leukocytes, the greater was the patient's resistance against the invading organism, whereas the higher the percentage of neutrophils, the severer was the character of the infection. If the leukocytes were comparatively low in number and the percentage of neutrophils was high, the infection was supposed to have overpowered the patient's resistance, and usually terminated fatally. Thus, with the total value of the leukocytes as an index of resistance and the percentage of neutro-

phils as an index of infection, the part of all the other leukocytic elements was considered passive. Any increase or decrease in these cells was supposed to depend on a concomitant change in the neutrophils. The monocytes, considered by Ehrlich and Naegeli⁴ as nongranular cells of myeloid origin, were believed to react biologically in direct proportion to any change in the neutrophils. The lymphocytes, on the contrary, though passive, acted in indirect proportion to any change in the neutrophils.

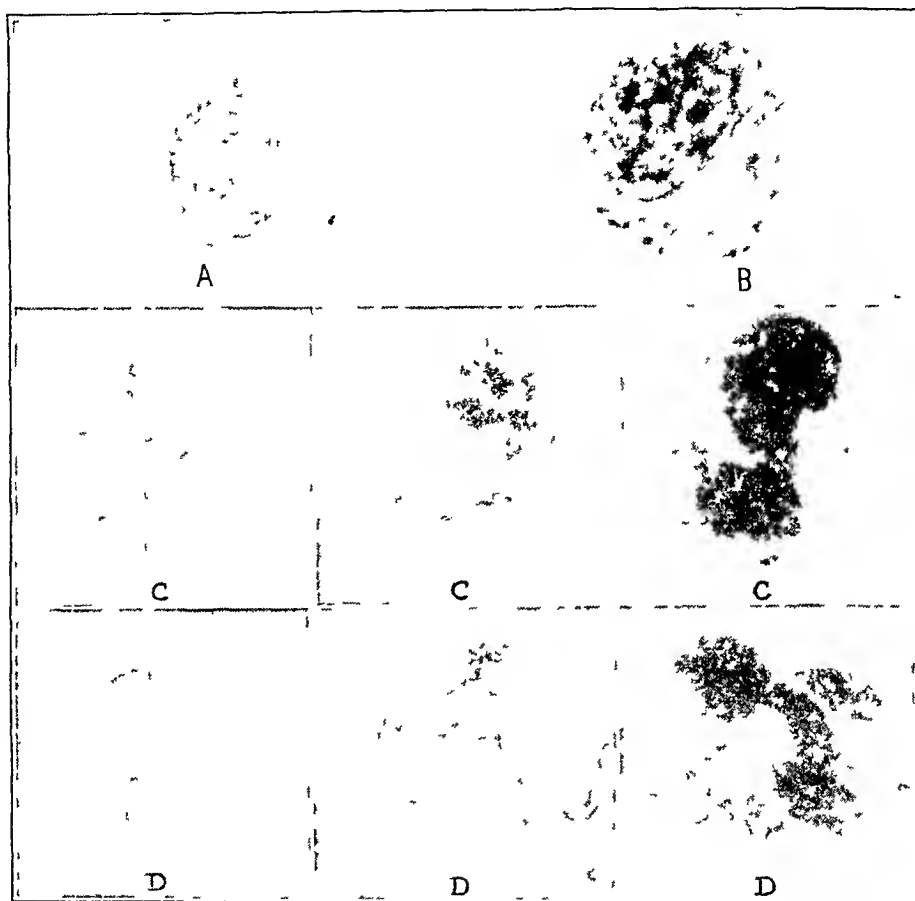


Fig 4—Photomicrographs of neutrophilic leukocytes *A*, a myeloblast, *B*, a metamyelocyte, *C*, forms of staff neutrophils, and *D*, forms of segmented neutrophils

As long as the interpretation of the observations of the blood in this series of cases was governed by these beliefs, numerous were the apparent discrepancies. Careful observations of numerous and serial examinations of the blood have encouraged the stand that although the neutrophils reflected in the blood stream in the course of any infection are an important unit in the reaction, they are not the sole active par-

⁴ Naegeli: *Blutkrankheiten und Blutdiagnostik*, ed 4, Berlin, Julius Springer, 1923

ticipants Instead of the invading agent, by means of its toxins, exerting a chemotactic force resulting in a neutrophilia, there is a definite chain of coordinated biologic components, each unit appearing on or leaving the center of the stage at a definite cue As each cellular system is called on to act, the others almost automatically recede into the background, to reappear when necessary Thus, the bone marrow, the reticulo-endothelial system and the lymphatic system are called into action

The first system to be drafted into service with the onset of an acute infection is the neutrophil The bone marrow, which has been steadily at work manufacturing its usual quota of segmented neutrophils (from 70 to 75 per cent) and nonsegmented or staff cells (from 3 to 5

TABLE 4—*Classification of Infections According to the Percentage of the Staff Cells**

	White Blood Cells	Neutrophils							
		Myelocytes	Metamyelocytes	Staff Cells, per Cent	Segmented, per Cent	Basophils, per Cent	Eosinophils, per Cent	Lymphocytes, per Cent	
Normal	From 5,000 to 9,000			3 to 5	60 to 70	0.5 to 1	2 to 5	20 to 30	4 to 8
1 Mild	9,000		1	5	68			20	6
2 Moderate	10,200		2	10	67			20	1
3 Severe	28,400		1	33	50			15	3
4 Very severe	36,400			41	47			10	2 Patient died
	13,000			79	17			4	
	4,000			59	17			24	

* The average blood pictures to be found in acute infections of varying severity are tabulated As a rule, a severe infection will pass through all of the indicated stages from the height of the illness to the period of recovery The three examples employed in the fourth phase died because of overwhelming infections

per cent), is suddenly called on to furnish more cells If the demand is mild, the bone marrow is able to increase its shipments, and there is a resultant increase in the leukocytes in the form of mature neutrophils The nonsegmented or staff neutrophil may or may not be slightly increased However, when the call on the bone marrow is too great for its normal productive forces, a moderate to marked increase in the staff forms occurs This increase depends on the severity of the infection Often at the crisis in a case of pneumonia, the staff cells may be as high as 70 per cent or more of the entire number of leukocytes While this neutrophilic phase is in action, one observes that all of the eosinophils have left the circulation, that the monocytes are also gone or are present in very small numbers, and that the lymphocytes have decreased to from 1 to 10 per cent With the surgical removal of the infectious focus, or the repulsion of the bacteria by the human host, the neutrophilic phase suddenly leaves the center of activity and is replaced

by monocytes. Though this cell was at one time believed to be of myeloid origin, because of its biologic reactions and supravital staining affinities, numerous investigators have agreed that it actually represents a definite cellular system of hematopoiesis. As a rule, the monocytes are showered into the blood stream at the moment the peak of the staff cells starts to recede. In chronic and subacute cases, however, the monocytes will be found in increased numbers until the period of convalescence. The monocytic phase is of short duration, and unless the blood is examined at frequent intervals during the crisis, this phase will be missed. The last system to be called into play is the lymphatic. The lymphocytes, which during the height of the infection drop from their normal percentage of between 25 and 30 per cent to between 1 and 10 per cent, gradually rise in number, and during convalescence will often be found to be present in numbers as high as from 50 to 60 per cent. That the increase in the various cellular elements at these different intervals of an infection is not a passive process, dependent on an increase or a decrease in the number of neutrophils, can be seen by the signs of marked hyperactivity of the monocytes and lymphocytes. Monocytes showing vacuoles, phagocytosed remnants and mitoses are often encountered. Lymphocytes also show their hyperactivity by the presence of Rieder forms, Turck irritation cells and double nuclei.

SUMMARY

A careful review of the data prepared from about 20,000 examinations of the blood performed during the past five years yields the following conclusions:

1. The leukocytosis caused by acute infections is primarily the result of stimulation of the bone marrow. This reaction of the bone marrow is a nonspecific, biologic phenomenon that depends not only on the type of organism, but on the degree of irritation caused by bacterial toxins. The neutrophilia thus brought about shows a varying percentage of immature or staff neutrophils, depending on the severity of the toxemia and the ability of the bone marrow to respond to it. A careful morphologic examination of serial blood films taken during the course of an infection will demonstrate that

- (a) The peak of the staff count and the height of the infection usually coincide.

- (b) The peak of the staff count drops as soon as the infectious process is removed or overcome.

- (c) The persistence of a high staff count usually means a complication.

- (d) The persistence of a high staff count may mean that the infection is becoming subacute or chronic.

(e) The persistence of a high staff count without the possibility of removing the infectious focus usually indicates a fatal outcome

(f) The presence of a high staff count early in the course of lobar pneumonia usually is indicative of a fatal outcome

(g) The curve of the daily staff count is more accurate as an indication of the course of the infection than the chart of the temperature

(h) The staff count is more reliable than the leukocytic or polymorphonuclear count

2 Concomitant with the sharp drop in the staff count are a sudden increase in the number of monocytes and a return of the eosinophils into the circulation

3 In subacute or chronic infections, one finds a persistence of an elevated staff count with an increased number of monocytes and lymphocytes

4 Lymphopenia, which is present during the neutrophilic phase of acute infections, is replaced by lymphocytosis during the period of convalescence and healing. In subacute or chronic infections, the lymphocytes are usually increased

For those who employ this method of morphologic examination of the blood, it is extremely important to bear in mind that a single report of a high staff count does not spell a fatal prognosis. (In case 1 the staff count rose as high as 70 per cent of the differential count, with eventual recovery.) Daily morphologic examinations of the cell are of inestimable importance, for it is on the curve that the prognosis of the case depends. It must be remembered that the changes in the blood are always to be considered conjointly with the complete clinical findings. It is also advisable to bear in mind that outstanding changes in the blood cannot be disregarded because of the lack of clinical corroboration. Nevertheless, it is also true that a definite clinical picture cannot be negated by a lack of confirmatory hematologic observations. Last, but not least, it must always be borne in mind that examination of the blood cannot always be employed as a means of diagnosis. Although one usually finds a definite biologic chain of leukocytic interreaction in infections, every now and then, owing to some unrecognizable cause, the blood picture fails to indicate the patient's condition. One must not forget that even now the reason for the appearance of the various cells in the circulation is not known, and therefore no cause can be ascribed for their failure to appear. These hematologic failures must not serve to discourage the clinician or the laboratory worker, but should spur him on to deeper and more exact observations. Careful serial morphologic examinations in which use is made of the neutrophilic subclasses are of inestimable value in the hematologic study of all infectious diseases.

UNEXPLAINED GASTRIC ANACIDITY *

W SCOTT POLLAND, M D

AND

ARTHUR L BLOOMFIELD, M D

SAN FRANCISCO

With the introduction of histamine as a stimulus to gastric secretion it became necessary to revise preexisting ideas about gastric anacidity, since it was found that many people who failed to secrete free acid after a meal of bread, gruel or alcohol gave a normal or nearly normal response after stimulation by the more powerful agent. In fact total inability of the stomach to secrete acid now appears to be an uncommon condition, which is in contrast to the older observations that indicated that anacidity was to be found in from 5 to 40 per cent of people without obvious gastric disease.¹

During the past few years we have studied the gastric secretion of about five hundred persons, with and without digestive symptoms, by means of the histamine test. Failure to produce free hydrochloric acid (when tested with dimethyl-amino-azobenzene) occurred in the following conditions: (1) invariably in cases of typical pernicious anemia, (2) frequently in cancer of the stomach, and (3) occasionally in the group of patients with diarrhea, anemia and stomatitis who may respond typically to feeding with liver as do patients with pernicious anemia. In addition to the aforementioned cases, anacidity has been present in a certain number of people with or without mild digestive symptoms, and for lack of a better term we have designated this condition as "unexplained anacidity." This article deals with this disorder.

Twenty-five cases of unexplained anacidity have been encountered. The frequency of this observation in relation to normal findings cannot be stated, as we were dealing with miscellaneous material. However, most of the "unexplained anacidities" were detected incidentally during routine tests and were not anticipated on the basis of the symptoms presented by the patient. Certainly the condition is an infrequent one.

Before classifying a case as "unexplained anacidity" every attempt was made to eliminate other clinical explanations. In no case was there sufficient evidence to make one consider seriously the diagnosis of pernicious anemia or cancer, and the patients were not sufficiently depleted

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* From the Department of Medicine, Stanford University Medical School

1 Keefer, C S and Bloomfield, A L. The Significance of Gastric Anacidity, Bull. Johns Hopkins Hosp. 39: 304, 1926

by febrile, malignant or other grave disease to allow one to infer a functional inhibition of proper secretion. Furthermore, in several cases repeated tests gave the same result. Gastritis is a tempting term with which to label obscure gastric disorders, and its possible relation to the present group of cases will be discussed later. However, none of the traditional causes that are alleged to lead to damage to the gastric mucosa were prominent in this series, namely, the excessive use of alcohol, hot or spiced foods or drugs.

Adequate solution of a problem such as the present one obviously depends on histologic study of the organ the function of which has been examined *intravital*. But the difficulties are great when one considers the rarity of "unexplained" anacidity, and so far none of our patients have come to anatomic examination. There are no convincing data in the literature, since as yet no one has reported a series of this sort in which the histamine test has proved that an abolition of gastric secretion really existed.

THE CLINICAL PICTURE OF ANACIDITY

In view of the facts to be brought out by the analysis of our cases, it is necessary to mention briefly the symptomatology that has been associated in the literature with gastric anacidity. While every writer has recognized the latent occurrence of the condition, a certain group of phenomena have none the less been frequently attributed to it, especially diarrhea and mild symptoms of indigestion. However, in a hundred consecutive cases of acidity tested with the Ewald meal, Keefer and Bloomfield¹ were unable to detect characteristic symptoms, although doubtless their series was inadequate as histamine had not been used and in many of the cases the patients surely would have been capable of secreting freely under the more powerful stimulus.

METHODS AND MATERIAL

As pointed out, the present series consisted of miscellaneous hospital patients, most of whom did not have a primary digestive condition. The tests were done as a routine, and many of the subjects were selected to serve in determining normal standards of gastric function. In this group the discovery of anacidity was entirely unexpected.

The procedure² consisted of introducing a small tube into the stomach after the patient had fasted for at least twelve hours. The fasting secretion was withdrawn, and 0.1 mg. of histamine per ten kilograms of body weight was given hypodermically. The secretions were then aspirated over successive ten minute periods. As a rule, only a few cubic centimeters of mucoid material was obtained.

² Bloomfield, A. L., and Polland, W. S. The Diagnostic Value of Studies of Gastric Secretion, *J. A. M. A.* 92:1508 (May 4) 1929.

RESULTS

In the accompanying table the main diagnostic facts of the series are summarized, but a number of points may be discussed in detail

Age—A consideration of the ages of the patients immediately throws light on one of the important problems of anacidity. Only two patients (cases 7 and 8) were under 40 years of age. The youngest patient in the series was 29 years old. It appears that anacidity is not as a rule purely congenital. Whether its development is due to external causes or whether some constitutional element enters in, cannot be said at present. This point will be studied further.

Clinical Diagnoses of Cases of Anacidity

Case	Age	Sex	Clinical Diagnosis
1	58	M	Tinnitus, congenital neurosyphilis
2	50	F	Migraine, psychoneurosis, undernutrition, anemia
3	42	F	Gas, constipation, indefinite abdominal pain
4	67	M	Arteriosclerosis, chronic prostatitis
5	75	M	Arteriosclerosis myocarditis
6	65	M	Pulmonary tuberculosis
7	39	F	Psychoneurosis
8	44	M	Chronic arthritis, iritis
9	60	M	Arteriosclerosis, hypertension, spondylitis, glaucoma
10	55	M	Arteriosclerosis hypertension
11	47	F	Psychoneurosis, dietary deficiency, acne rosacea, anemia
12	42	F	Psychoneurosis, drug addiction
13	44	M	Indigestion
14	62	M	Cholelithiasis
15	49	M	Erythema multiforme
16	40	M	Aortic insufficiency
17	56	F	Mucous colitis
18	29	M	Acne rosacea
19	45	M	Acute polyarthritis (convalescent)
20	60	M	Indigestion
21	67	M	Abdominal pain (unexplained)
22	48	M	Epilepsy
23	42	M	No disease
24	49	M	Chronic fibroid tuberculosis, indigestion
25	65	F	Indigestion

Sex—There were eighteen men, and seven women, 72 and 28 per cent, respectively. However, more men than women come to the clinic, and more tests are made on men. It may be assumed that there is no great difference in sex incidence.

Familial History of Cancer, Stomach Trouble, Anemia or Neurologic Disorders—Definite statements on these points were available in twelve cases. In no instance was the patient aware of the occurrence of the aforementioned disorders.

Occupation—A miscellaneous group of occupations was represented, including housewife, barber, carpenter, cement worker, kennel caretaker, salesman, sheriff, surveyor, student, teamster and tailor.

Previous Diet—Specific inquiries were made as to patient's dietary habits. In only one case (case 11) was there a suggestion of dietary

inadequacy For the past three years this patient had subsisted largely on cereals and toast

Alcohol, Drugs and Gastric Irritants—There was no history in any case of excessive indulgence in or use of alcohol, drugs and gastric irritants, except in the following cases In case 4 the patient had drunk 1 gallon (4.5 liters) of whisky daily until prohibition and none since, in case 9 the patient used to drink much whisky but had had none recently, in case 10 the patient drank from one to two glasses of wine with each meal, in case 21 the patient had drunk considerably many years previously It seems most unlikely that any special factor of gastric irritation was of etiologic importance in these cases

Gastro-Intestinal Symptoms—A special study was made of gastrointestinal symptoms, since it has been thought by some that a clinical association exists between gastric anacidity and diarrhea and indigestion In regard to the movement of the bowels, twelve patients had normal habits, ten were habitually constipated and in only two was there an indication of abnormal looseness In case 24 the patient had had frequent attacks of moderate looseness of the bowels in the last six years, and in case 4 the patient usually had from two to three movements daily Fourteen, or 56 per cent, of the patients had never had indigestion or other gastric symptoms, and three, or 12 per cent, complained only of gas—a symptom so common in general practice as to have no special meaning Definite gastric complaints were present in eight, or 32 per cent of the patients of this series in case 2, periodic migraine with nausea and vomiting, in case 6, vomiting after the ingestion of large amounts of food, in case 9, the feeling that the stomach could not hold much, in case 10, a heavy feeling with gas, relieved by food, in case 13, gas and sour stomach, in case 17, an occasional indefinite abdominal pain and gas after meals, in case 25, gas and indigestion, and in case 11, a burning sensation in the stomach with belching

In summary, the majority of these patients had no definite gastrointestinal symptoms The remainder presented a variety of mild complaints without specific characteristics and not essentially different from what one might encounter in persons with normal gastric secretion It would be difficult to assume that the defect in gastric secretion per se produces definite symptoms, a conclusion that was reached by Bloomfield and Keefe in their previous study

Evidences of Pernicious Anemia and Neurologic Changes—Neurologic changes suggestive of the combined sclerosis of pernicious anemia were not detected in any member of the series, and from the standpoint of physical examination, there was no other evidence of pernicious anemia, such as smooth tongue or palpable spleen The blood count

and blood picture were not unusual, except in two patients. In case 2 examination of the blood showed red cells, 3,700,000, hemoglobin, 76 per cent, white cells, 6,200 with a low percentage of neutrophils (37 per cent). There was slight anisocytosis and poikilocytosis. Follow-up studies will show whether more definite change in the blood develops. In case 11 examination of the blood showed red cells, 3,700,000, hemoglobin, 70 per cent, white cells, 5,700. The differential count and the morphologic characteristics were normal. The Wassermann test gave negative results in every case.

Roentgen Studies—Roentgenograms of the gastro-intestinal tract were made in twenty cases, in nineteen cases nothing important was found. In case 20 there was an irregularity of the greater curvature extending from the cardia almost to the antrum. Cancer seemed unlikely because the whole stomach was flexible and freely movable.

Gastric Analysis—In a previous paper,³ we described the character and the composition of the gastric secretion in conditions in which there was a failure to respond to histamine such as cancer and pernicious anemia. The findings in the present series differed in no respect, and the material obtained from the stomach consisted of a few cubic centimeters of mucoid material which gave a yellow color on testing with dimethyl-amino-azobenzene.

Clinical Diagnosis—One of the most important points under consideration was whether the gastric anacidity bore any real relationship to the patient's outstanding disease or whether it was an insignificant and incidental finding. The final diagnoses are given in the accompanying table. In sixteen cases (64 per cent) there seem to be nothing to explain the defect of gastric secretion. Five patients had mild digestive symptoms in no way different from those encountered in any hospital population, it cannot be said whether or not these symptoms were related to the anacidity, but it seems unlikely. In cases 2, 11, 20, 24 and 25 the patients had definite gastro-intestinal symptoms, and in case 25 the patient was relieved by hydrochloric acid.

COMMENT

It appears that failure to secrete acid (or indeed any actual gastric juice) occurs in a certain number of persons, apart from the well known associations of anacidity, such as pernicious anemia and cancer of the stomach. It may be estimated that such "unexplained anacidities" are encountered in from 3 to 5 per cent of the patients in a medical clinic. In the present series the disorder was distinctly one of middle

³ Bloomfield, A. L., Roberts, A. M., and Pollard, W. S. The Composition of the Gastric Secretion in Cases of Anacidity, *Tr. A. Am. Physicians* 43: 242, 1928.

and old age, a finding which suggests that it is acquired rather than congenital, but beyond this no relation was found to age, sex, occupation, diet or habits. It has not been possible to define any symptom-complex that is clearly associated with the gastric disorder. This point deserves especial emphasis in view of alleged "anacidity diarrheas" and other syndromes that have been described from time to time. In the present series most of the cases were asymptomatic as far as the gastro-intestinal tract was concerned, in the few cases in which digestive symptoms occurred they presented no specific features. In only one instance was there evidence that the administration of hydrochloric acid may have had some beneficial effect.

The present report really sets the problem rather than answers it, and it remains to show the underlying lesion responsible for the disorder of secretion and the effect of the presence of complete anacidity on ultimate general health. A further question of special importance is whether anacidity of this sort is followed in a large percentage of cases by the development of cancer of the stomach, a point that has recently been raised again by Hurst⁴ and by us⁵.

With these problems in mind, an "anacidity clinic" has been started. The patients are seen periodically, they are interviewed and examined, and roentgenograms and gastric analyses are made repeatedly. If any of the patients die, it is hoped that pathologic examination will be possible. At any rate a further report is planned after a sufficient interval, probably five or ten years, has elapsed.

⁴ Hurst, A. F. The Precursors of Cancer of the Stomach, *Lancet* **2** 1023, 1929.

⁵ Polland, W. S., and Bloomfield, A. L. Gastric Secretion in Cancer of the Stomach, *Bull. Johns Hopkins Hosp.* **46** 307, 1930.

METABOLISM IN PNEUMONIA

II THE MECHANISM OF THE RETENTION OF CHLORIDE IN PNEUMONIA ¹

ISIDOR GREENWALD, PH D

NEW YORK

Although the knowledge of a lessened concentration of chloride in the urine of patients with fever ¹ seems to have antedated Redtenbacher's ² report, he appears to have been the first to have definitely connected pneumonia with a regularly diminished excretion of chloride. Ever since then, the subject has attracted considerable attention. The original observations have been amply confirmed and extended ³. Many studies on the metabolism of patients with pneumonia have been made, but, aside from the changes due to the increased protein catabolism, no change comparable to that in the excretion of chlorine (and sodium) has been observed, nor have these numerous investigations furnished a satisfactory explanation for the observed changes in excretion of the chloride.

One of the first hypotheses to have been advanced in explanation of this condition appears to be that of Traube, ⁴ who suggested that the low excretion of chloride was due to a failure of absorption from the intestine. This was shown to be false by Rohmann, ⁵ Terray, ⁶ Schwarz ⁷ and von Moraczewski, ⁸ who pointed out that the feces obtained during the period of diminished excretion of chloride in the

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1 Simon, J F. *Animal Chemistry*, translated by G E Day, London, 1846, vol 2, p 208

2 Redtenbacher, W. *Ztschr d kaiserliche-konigliche Gesellschaft d Aerzte zu Wien* 2 373, 1850

3 For a review of the earlier literature see Hutchison, R. *J Path & Bact* 5 406, 1898

4 Traube L. *Symptome der Krankheiten des respiratorischen und circulatorischen Apparat*, Berlin, 1867, quoted by Hutchison (footnote 3)

5 Rohmann, F. *Ztschr f klin Med* 1 513, 1880

6 Terray, P. *Ztschr f klin Med* 26 346, 1894

7 Schwarz. *Wien med Bl*, 1895, no 49, quoted by von Hosslin. *Deutsches Arch f klin Med* 93 404, 1908

8 von Moraczewski, W. *Virchows Arch f path Anat* 55 11, 1899

urine contained no more than the usual amounts of chlorine. There was, therefore, no failure of absorption or any abnormally large excretion of chloride into the intestine.

Schwenkenbecker and Spitta⁹ collected and analyzed perspiration from a number of normal and febrile persons. In the one patient with pneumonia whom they studied, the amount of chloride in the perspiration was only a little more than that in the normal controls. The greatest amount of chloride was found in the profuse perspiration of patients with tuberculosis, and even then it was only 0.02 Gm per kilogram of body weight greater than the normal amount. The chloride that disappears from the urine is, therefore, not to be found in the perspiration.

According to Terray,⁴ Schwaiz⁷ and Hutchison,³ the sputum of patients with pneumonia contains no more than about 0.5 Gm of sodium chloride a day. Sunderman¹⁰ found values up to 0.88 Gm in some of his patients, but even this exceptional amount is not comparable to that which fails to appear in the urine. The reality of the retention of chloride in the urine must be regarded as established.

In fact, Redtenbacher,² in 1850, and Beale,¹¹ in 1852, believed this to be the case, and the latter regarded his analyses as establishing the fact of the retention of chloride in the pneumonic lung. That the pneumonic lung, because of its greater weight, does contain more chlorine than does the normal lung has been well established by the work of Terray,⁶ Hutchison,³ von Moraczewski,⁸ Meillère¹² and Peabody,¹³ but the amount so retained seems rarely to be more than 2 Gm, and is, as Hutchison pointed out, probably never more than 6 or 7 Gm. Since the total amount retained often greatly exceeds this, the amount contained in the consolidated lungs cannot, alone, account for the retention.

It was natural to look for the retained chloride in the blood. However, the results of numerous analyses, beginning with those of Runeberg¹⁴ and Laudenheimer,¹⁵ showed that the concentration of chloride in the blood of patients with pneumonia was not only not greater but was actually somewhat lower than that in the blood of normal persons.

9 Schwenkenbecker and Spitta. *Arch f exper Path u Pharmacol* **56** 284, 1907.

10 Sunderman, F. W. *J Clin Investigation* **8** 313, 1929.

11 Beale, L. S. *Tr Med-Chir Soc, London* **35** 325, 1852.

12 Meillere, M., reported by Achard, C., and Loepier, M. *Compt rend Soc de biol* **53** 346, 1901.

13 Peabody, F. W. *J Exper Med* **17** 71, 1913.

14 Runeberg, J. W. *Deutsches Arch f klin Med* **35** 266, 1884.

15 Laudenheimer, R. *Ztschr f klin Med* **21** 513, 1892.

Hutchison was inclined to minimize the importance of this observation. He wrote ¹⁶

The diminution of the chloride in the urine however, is out of all proportion to the degree of diminution found in the blood. In the latter it only amounts to a decigramme or less in every 100 cc whereas in the urine the diminution may go to the length of total disappearance. It seems almost incredible that the kidney function can be so delicately adjusted that such a slight fall in the amount of sodium chloride in the blood should lead to an entire cessation of its excretion.

The conception of a threshold value for chloride in the urine corresponding to a concentration of chloride in the plasma below which no secretion into the urine would occur was apparently unknown to him.

The idea of a renal threshold for chloride as a definite concentration of chloride in the blood or plasma below which no excretion into the urine takes place was, it is true, overthrown by Aitken,¹⁷ but his work definitely established the renal threshold as "a region in which the relation of renal excretion to plasma concentration changes rapidly," a conception that Hutchison regarded as "almost incredible."

But if the retained chloride is not present in the lungs or in the blood, where is it? It seemed likely that the muscles and liver, because of their bulk, might contain appreciable quantities. Also, since Padtberg¹⁸ showed that in dogs the concentration of chloride of the skin was considerably increased after the intravenous injection of sodium chloride, it was possible that, in patients with pneumonia, also, some of the retained chloride was deposited in the skin. But analyses of muscle, liver and other tissues by von Moraczewski¹⁹ and Hutchison,³ and of the skin by Santini²⁰ and Peabody,¹³ failed to show any appreciable accumulation of chloride.

It has frequently been suggested that the disturbance is not primarily in the metabolism of chloride but in that of water. It is supposed that, for some reason or other, water is retained and that sodium chloride is retained only in sufficient quantity to preserve the proper osmotic pressure and ionic equilibrium. That there may be a marked retention of water during pneumonia is unquestioned, for patients have been known to gain weight in spite of the marked loss of nitrogen. Accurate data on the extent of the retention of water are not plentiful, in fact, only Sunderman's data appear to be at all complete. He showed that even when the retention of water was most marked, as

16 Hutchison (footnote 3 p 427)

17 Aitken R S J Physiol **67** 199, 1929

18 Padtberg J H Arch f exper Path u Pharmacol **63** 60, 1910

19 von Moraczewski W Ztschr f klin Med **23** 483, 1897

20 Santini A Riforma med **19** 477, 1903, quoted by Peabody (footnote 13)

in the case of his patient B₇, the maximum amount of chloride that could be so accounted for was only one third of the amount retained

It is worthy of note that the retention of chloride generally continues for a few days after the crisis of the disease. The postcritical increase in the excretion of nitrogen, which is, in all probability, due to resorption in the lung, is much more prompt than the increase in excretion of chloride. It would seem that some of the chloride contained in the consolidated lung is transferred to other tissues. Finally, there comes a period of negative chloride balance. The assumption has been natural that this represents a return to the normal concentration of chloride in the unknown tissues that had previously been retaining chloride. However, it is usually found that this loss of chloride is not even as great as the amount retained while the patient was under observation, and that the negative balance is accompanied by diuresis and loss in weight. In other words, the postcritical loss of chloride seems due to that part of the previous accumulation that had accompanied the retention of water. The fate of the remainder of the chloride remains unknown.

Roehrich and Wiki²¹ claimed to have observed a second rise in the retention of chloride from the twenty-fifth to the twenty-eighth day of the disease, after convalescence was well advanced. This interesting observation has not yet been confirmed by others.

Before proceeding to a discussion of my own experiments, it seems necessary to discuss in some detail two recent papers on the subject.²² Wilder and Drake stated among their conclusions that

In infants with primary pneumonia we find a negative base and chloride balance if the intake of these ions is low, and a markedly positive balance if the intake is high.²³

And Sunderman said

The present studies of the chloride balance do not support the view that pneumonia is characterized by a retention of chloride during the precritical period but rather that it is characterized during the precritical period by a diminished capacity of the body to conserve chloride on a low intake of chloride and a diminished capacity to excrete chloride on a high intake of chloride. After the crisis the chloride balance becomes restored to normal from whichever deviation had earlier developed.²⁴

These conclusions are in such striking agreement that, coming, as they do, from different laboratories, they carry weight. Nevertheless,

21 Roehrich, A. W., and Wiki, B. *Rev. méd. de la Suisse Rom.* **20** 312, 1900.

22 Sunderman (footnote 10). Wilder, T. S., and Drake, T. G. H. *J. Clin. Investigation* **7** 353, 1929.

23 Wilder and Drake (footnote 22, second reference, p. 363).

24 Sunderman (footnote 10, p. 329).

it is difficult to imagine how the metabolic disturbance in pneumonia can be so entirely different in patients receiving small amounts and in those receiving greater amounts of chloride. It would seem that the disturbance in metabolism must be the same in both groups.

Wilder and Drake presented the results of but one experiment on the metabolism of a child on a low intake of chloride. This was "nearly zero" or "zero"²⁵. Under such circumstances, it is not surprising that the child lost chloride. No other result could possibly have been expected. In five days, the total loss was 0.01425 equivalents, or 0.505 Gm of chlorine. But, during these same five days, in spite of an apparent retention of 1,820 Gm of water, the child lost 785 Gm in weight. Assuming this loss to have been muscular tissue, it would have contained about 0.505 Gm of chlorine²⁶. The agreement is striking.

Wilder and Drake did not give data for the excretion of nitrogen. Calculations cannot be very wrong, however, if it is assumed that the loss of 785 Gm in weight and the indicated retention of 1,820 Gm of water were accompanied by the catabolism of approximately 2,600 Gm of body tissue, containing approximately 1.6 Gm of chlorine. This was as fully available for excretion as the same amount of chlorine ingested with food might have been. Since only 0.5 Gm was excreted, it is obvious that approximately 1.1 Gm was retained.

Sunderman reported data on the intake and output of nitrogen. All of his patients with pneumonia lost nitrogen and therefore catabolized body tissue. These tissues contained chloride, and, if this chloride was not found in the excretions, it was as truly retained as any chloride that might have been fed to the patient. In calculations on the retention of chloride, it is not sufficient to consider merely the body weight, as did Sunderman. It is conceivable that a patient might catabolize 1 Kg of body tissue per day and retain an equal amount of water. The kilogram of body tissue would furnish about 0.7 Gm of chlorine. If the intake of chlorine were 1 Gm and the excretion 1.2 Gm, there would be an apparent loss of 0.2 Gm, whereas, in truth, there would be a retention of 0.5 Gm.

Examination of Sunderman's results indicates that something of this sort actually occurred. The seven precritical days on which he based his conclusions include one each in cases B₁ and B₂, two in B₄ and three in B₅. The losses of nitrogen on these days varied from 7 Gm in a boy weighing 26.5 Kg to 27 Gm in a man weighing 61 Kg. It is difficult to calculate the exact amount of chloride correspond-

²⁵ Wilder and Drake (footnote 22, text, p. 356 and table, p. 357).

²⁶ Katz, J. *Arch f d ges Physiol* **63** 1, 1896. Magnus-Levy, A. *Biochem Ztschr* **24** 363, 1910.

ing to this amount of nitrogen According to Benedict,²⁷ in persons during fasting, there is a steady fall in the ratio of chlorine to nitrogen in the urine as the fast is continued Moreover, particularly during the first days of the fast, this ratio varies considerably in different persons Sunderman's studies were made on patients between the sixth and ninth days of the disease At this time, the losses of nitrogen were, approximately, twice as great as those in normal persons during fasting For the purpose of calculating the proper ratio of chlorine to nitrogen it might be urged that the ratio that obtains between the sixth and the ninth day of a fast in normal persons should not be taken, but, instead, that existing between the twelfth and the eighteenth day

Reference to Benedict's compilation of the data on fasting persons shows that these are available only for his own experiment on L, and for four experiments on Succi Of the latter, three show values

TABLE 1—*Excretion of Chlorine and Nitrogen in Patients During Fasting**

Days of Fast	Subject L			Succi		
	Nitrogen, Grams	Chlorine, Grams	100 Chlorine Nitrogen	Nitrogen, Grams	Chlorine, Grams	100 Chlorine Nitrogen
12	10.13	0.31	3.1	7.88	0.405	5.14
13	10.35	0.32	3.1	3.86	0.230	5.96
14	10.43	0.26	2.5	5.87	0.119	2.05
15	8.46	0.16	1.9	5.66	0.137	2.42
16	9.58	0.14	1.5	6.05	0.113	1.87
17	8.81	0.12	1.4	6.78	0.130	1.91
18	8.27	0.15	1.8	6.00	0.258	4.30
Average	9.43	0.21	2.2	6.01	0.199	3.01

* Data from Benedict (footnote 27)

that are much higher than those in the fourth experiment (Florence) In order to secure minimal values, the data for Benedict's subject L and for Succi's fast in Florence are given in table 1 From these data, it is apparent that the minimal amount of chlorine that must have been derived from the catabolism of body tissue in Sunderman's experiments was 0.022 Gm, or 0.62 milliequivalents, per gram of nitrogen lost

The pertinent data from Sunderman's tables for the seven pre-critical and the three critical days on which he bases his conclusions have been collected in table 2 The fourth column, giving the chlorine equivalent to the nitrogen lost, on the basis of 0.62 milliequivalents of chlorine for each gram of nitrogen, and the fifth column, giving the sum of this and the intake of chlorine as the total chlorine available for excretion, have been inserted As is evident from the last column,

27 Benedict, F. G. A Study of Prolonged Fasting, Washington, Carnegie Inst., 1915

the balance was positive on every day but three, and on one of these the negative balance was small, 0.5 milliequivalents. In the other two instances, the negative balance was followed (B_4), or preceded and followed (B_5), by retentions of chlorine nearly sufficient to balance the losses.

In this calculation it is true that no account has been taken of the chloride that may have been lost in the perspiration. Sunderman mentioned that the highest value of sodium chloride per day that he actually observed was 0.27 Gm., although he regards this as almost certainly too low, because of faulty technic. He did not state whether or not this value was taken in a patient on a diet high or low in chloride or before or after the crisis of pneumonia.

TABLE 2—*Recalculation of the Balance of Chlorine in Patients Observed by Sunderman*

Case	Nitrogen Lost, Gm	Intake of Chlorine M Eq	Chlorine Equiva- lent to Nitrogen Loss M Eq	Total Chlorine Available for Excretion M Eq	Output of Chlorine					Balance M Eq
					Urine M Eq	Feces M Eq	Sputum M Eq	Blood M Eq	Total M Eq	
B_1	13	17	8.0	25.0	0.2	2.5	5.1	3.0	10.8	+14.2
	16	17	9.9	26.9	0.0		11.6	4.6	16.2	+10.7
B_2	17	36	10.5	46.5	36.9		2.8	4.2	43.9	+2.6
B_4	27	22	16.7	38.7	39.5			5.0	44.5	-5.8
	26	25	15.5	40.5	31.6	0.6	1.8	1.8	35.8	+4.7
	27	25	16.7	41.7	37.6		1.0	3.6	42.2	-0.5
B_5	7	26	4.3	30.3	22.9	2.1	0.1	2.0	27.1	+3.2
	9	22	5.6	27.6	30.2	0.4	2.9		33.5	-5.9
	7	19	4.3	23.3	13.6		4.6	3.1	21.3	+2.0
	10	19	6.2	25.2	13.2	3.0	3.8		20.0	+5.2

Schwenkenbecker and Spitta,⁹ whose work was cited by Sunderman, obtained, as has already been stated, values as high as 2.7 Gm. per day per hundred kilograms of body weight. However, this was in a patient with tuberculosis. The only patient with pneumonia studied by them excreted 0.73 Gm. per hundred kilograms of weight on the day before the crisis, 0.95 Gm. on the day of the crisis and 0.73 Gm. on the following day. For patients such as Sunderman's B_4 (heaviest in weight), an excretion of 0.73 Gm. of chloride per hundred kilograms of weight would be about 0.445 Gm., or 7.6 milliequivalents, per day. It is true that this is sufficient to turn the retentions into losses in every case but in B_1 . But the calculations in the table have been based on the minimal value of 0.62 milliequivalents of chlorine for each gram of nitrogen lost. If the ratio of 1 milliequivalent per gram, which is lower than existed before the eighth day in any of Benedict's nine patients during fasting, is used, a retention of chloride would be indicated in every case.

Nothing has been said of Sunderman's consideration of the chloride found in the blood removed for analyses as part of the output of chloride. There is, in my opinion, little justification for such a consideration. This chloride was not excreted by the body but was removed from it, it is scarcely any more to be included in the "output" than would the chloride content of a finger be, had it, instead of a corresponding weight of blood, been removed for analysis.

That there is something wrong with Sunderman's reasoning is apparent from a consideration of the results in patient B₁. On two successive days, this patient excreted 17 and 20 Gm of nitrogen, resulting in a loss of 13 and 16 Gm of nitrogen, respectively. On these two days, he excreted only 0.2 and 0.0 milliequivalents of chloride in the urine, and, in the urine and feces, a total of 2.7 milliequivalents. A more effective retention of chloride cannot be imagined. Nevertheless, according to Sunderman's method of calculation, it is impossible to decide whether there was a retention or a loss of chloride on these days.

There is, therefore, no reason to believe that the disturbance in chloride metabolism is any different in patients on diets low in chloride than it is in those receiving liberal amounts of salt. The nature of the disturbance remains unknown.

EXPERIMENTAL DATA

In view of the difficulties inherent in experiments on the metabolism of patients with pneumonia, and because it was desired to study changes in the early stages of the disease, it was decided to experiment on animals. The dog appeared to be the most suitable animal for our purpose. Lamar and Meltzer²⁸ had induced pneumonia in dogs by intratracheal insufflation of pneumococcus cultures. The necessity for anesthesia proved to be an undesirable feature of their technic, and, after a few trials, it was discarded in favor of intratracheal injections of a centrifugated culture. In some cases, a pneumococcus autolysate prepared by the method of Parker and Pappenheimer²⁹ was also injected. In one experiment, the inoculation was made directly into the lung. A culture of type I pneumococcus, extremely virulent for mice, was used throughout.

It was found that the dogs refused to eat after inoculation and that food previously ingested or given by stomach tube was vomited. It was therefore decided not to feed the animals after the experiment had begun, but to collect the samples of urine during, and for a few days after, the fever, then to feed the dogs double rations to bring

²⁸ Lamar, R. V., and Meltzer, S. J. *J. Exper. Med.* **15** 133, 1912.

²⁹ Parker, J. T., and Pappenheimer, A. M. *J. Exper. Med.* **48** 695, 1928.

them back to their original weight, and, after several days on the standard ration, to repeat the experiment, sterile broth being used instead of the pneumococcus culture. The death of two of the animals made it impossible to carry out this program in full.

The content of nitrogen was determined by the method of Kjeldahl and that of chlorine by digestion of the urine with silver nitrate, nitric acid and a small amount of potassium permanganate, with subsequent titration of the excess silver nitrate.

PROTOCOLS

Dog 6, a female setter weighing 19 Kg., was kept on a diet consisting of 80 Gm of dried meat residue (obtained from the Valentine Meat Juice Company), 70 Gm of cracker meal, 10 Gm of vitavose (a wheat-germ preparation made by

TABLE 3—*Control Experiments The Excretion of Nitrogen and Chlorine in the Urine After the Injection of Sterile Broth*

Experiment 31				Experiment 32			
Date	Nitrogen Gm	Chlorine		Date	Nitrogen, Gm	Chlorine	
		Gross Gm	Net*			Gross Gm	Net*
3/1	7.93	0.883					
3/2	9.45	1.320		3/31	9.84	1.230	
3/3	9.71	1.070		4/ 1	11.69	0.780	
3/4	7.94	1.080		4/ 2	11.02	1.000	
3/5	2.05	0.179	0.091	4/ 3	4.35	0.368	0.277
3/6	5.19	0.411	0.383	4/ 4	1.83	0.402	0.360
3/7	2.56	0.220		4/ 5	3.88	0.952	0.910
3/8	4.41	0.376		4/ 6	5.10	0.502	

* This calculation was obtained by deducting the chlorine content of the broth injected into the animal.

E. Squibb & Sons), 20 Gm of bone-ash, 60 cc of maize oil, 1.50 Gm of salt and 1,000 cc of water. This animal was used for three experiments with pneumococcus cultures and for two control experiments. In order to facilitate discussion, the latter will be described first, though they were not, of course, the first to be performed. After the collection and analysis of the urine for four days during which the dog was kept on standard diet, food was withheld. On the first day of the fasting, March 5, 10 cc of sterile broth was injected intratracheally at 10:20 a. m. The rectal temperature, which had been 101.7 at 8:50 a. m., was 101.5 when a second injection of 12 cc of sterile broth was made at 1:20 p. m. The temperature was 101.7 at 2:30 and 102 at 4:30 p. m. On the following day, 17 cc of sterile broth was injected at 9:15 a. m., and the temperature fluctuated between 101 and 101.7.

This experiment was followed by one in which a pneumococcus culture was used (experiment 63, table 4). After the animal had recovered his normal body weight, urine was again collected for a few days while the animal received the standard diet. Food was again withheld, and 20 cc of sterile broth was injected intratracheally on April 3. This had no effect on the temperature. On each of

the following days, 10 cc of sterile broth was injected, with the same lack of effect on the rectal temperature

In experiments 61, 62 and 63, the same dog received cultures of a virulent type pneumococcus. The results of the analyses of the urine are summarized in table 4. The protocols of the individual experiments follow

EXPERIMENT 61—On February 11, a mixture of 5 cc of pneumococcus autolysate and 5 cc of a suspension of living pneumococci, each representing approximately 100 cc of an eighteen hour culture, was injected intratracheally at 10 10 a m. The temperature rose from 101.9 to 103 F at 1 p m, at which time 12 cc of a suspension representing 150 cc of a twenty-one hour culture was injected. At 3 p m, the temperature was 105.4 F and the dog was panting. Subsequent records of temperature and respiration, respectively, were 5 35 p m, 107.5 F. and 75, 6 35, 106.4 and 66, 12 midnight, 103 and 50, 8 15 a m, 102 and 22

The following day at 9 30 a m, 7 cc of a suspension equivalent to 200 cc of a sixteen hour culture was injected intratracheally. At 11 o'clock, the tempera-

TABLE 4—*Excretion of Nitrogen and Chlorine in the Urine*

Experiment 61				Experiment 62				Experiment 63			
Date	Nitro- gen, Gm	Chlorine		Date	Nitro- gen, Gm	Chlorine		Date	Nitro- gen, Gm	Chlorine	
		Gross Gm	Net † Gm			Gross Gm	Net † Gm			Gross Gm	Net † Gm
2/ 6	8.50	0.903		3/16	11.88	0.91		4/14	11.52	1.22	
2/ 7	10.53	0.714		3/17	11.48	1.29		4/15	12.31	1.33	
2/ 8	7.75	1.17		3/18	9.83	0.91		4/16	6.09	1.04	
2/ 9	9.64	1.03						4/17	13.55	1.26	
2/10	11.51	1.07									
2/11	6.40	2.64	2.54	3/19	4.04	1.00	0.91	4/18	3.70	1.24	1.19
2/12	4.63	0.29	0.26	3/20	4.97	0.27	0.20	4/19	4.58	0.11	
2/13	7.00	0.071		3/21	3.88	3.88	0.28	4/20	7.02	0.44	
2/14	6.11	0.029		3/22	2.54	0.32					
2/15	8.47	0.035		3/23	3.41	0.54					

* These experiments were performed on dog 6 in which a probable case of pneumonia was followed by recovery and in which subsequent inoculations produced but little effect.

† This calculation was obtained by deducting the chloride content of the culture injected into the animal.

ture was 102.4 F, and the respiratory rate was 50, at 12 10 p m they were 106 F and 75, respectively, at 2, 106 and 80, at 4, 104.4, panting, at 5 30, 104, panting, at 9 30, 104.3 and 30 and at 8 30 a m, 102 and 30

EXPERIMENT 62—At 10 a m on March 19, 12 cc of a suspension equivalent to 300 cc of a seventeen hour culture was injected into the dog intratracheally. There was no effect on the temperature until 1 20 p m, when 8 cc, also equivalent to 300 cc of a twenty hour culture, was injected. At 3 p m, the dog had a severe chill, and the temperature was 102.4 F. This rose to 104.6 at 4 45, but fell to 103.4 F at 6 p m.

The next morning the temperature was normal, and the injection of 16 cc of a suspension equivalent to 600 cc of an eighteen hour culture was without effect on the temperature. The experiment was repeated on the following day, with the same lack of success. The temperature remained unchanged.

EXPERIMENT 63—At 10 45 a m on April 18, 10 cc of a suspension equivalent to 600 cc of an eighteen hour culture was injected into the right lung of the same dog. At 12 45, the temperature had arisen from 100.6 to 104.8 F, the respiratory rate was 60, and the dog had a chill. The temperature was 105.2 F at 2 20,

105.8 at 4, 105.4 at 5 and 104.4 at 6. The respiratory rate all afternoon was about 40 per minute. At 8 10 p m the temperature was 102.6, and at 11 40 it was 102.1 F.

In view of the apparent resistance of the animal to these large doses of pneumococcus culture, it was believed that the serum might show marked protective action. However, the usual tests on mice made by Miss Georgia Cooper of the Department of Health of New York City showed that this was not the case.

EXPERIMENT 5 (table 5) —A female collie, weighing 13 Kg., was fed a mixture of 20 Gm of dried meat residue, 20 Gm of cracker meal, 10 Gm of vitavose, 15 Gm of bone-ash, 30 cc of maize oil, 1 Gm of salt and 700 cc of water. For several days, the rectal temperature fluctuated between 103 and 104 F, which was apparently normal for this dog. At 10 20 a m on February 11, a mixture of 5 cc of a pneumococcus autolysate and 7 cc of a fresh suspension, equivalent to 100 cc of an eighteen hour culture, was injected into the trachea. At 11 o'clock the temperature was 104.3 F, but at 12 o'clock it had reached 105, and the dog seemed quite sick. The temperature continued to rise, reaching 105.9 at 1 30, 105.8 at 3 and 160.4 F at 5 30 p m. At this time the respiratory rate was 55 per minute. The temperature then fell slowly to 105.8 at 6 35 p m, 104.8 at midnight and 103 F at 8 15 a m. Respirations continued to be rapid, the rate being between 50 and 58 a minute.

At 9 30 a m, on February 12, the dog received 6 cc of a suspension, equivalent to 200 cc of a sixteen hour culture, intratracheally. The temperature rose slightly, reaching a maximum of 105.2 at 12 noon, and then declined, to remain at about 104 F from 2 to 8 20 p m. The respiratory rate increased, reaching 70 at 8 20 p m and 80 on the following morning. It remained at this level all day, although the temperature was only 103.8 F.

On February 14, the temperature varied between 102.5 and 103.8 F, but the respiratory rate increased from 100 in the morning to 130 in the evening. The dog coughed a great deal, and the muscles of the neck and front legs twitched.

At 1 15 p m on February 15, a laboratory attendant found the dog in convulsions. When I saw the dog, the convulsion was over, she was lying on her side, the temperature was 103.8 F, and the respiratory rate 85. At 6 p m, the dog was standing up, staring at me without recognition, barking wildly and refusing to permit handling. After about five minutes, she became quiet, lay down and permitted the insertion of the thermometer. The temperature was 103.6 F, the respiratory rate 75, and the pulse rate 150. On February 16, at 10 30 a m, a convulsion suddenly developed, which lasted three minutes, and after which the dog was quiet. At 8 p m, the temperature was 102.9 F, the respiratory rate 75 and the pulse rate 150. An attempt was made to feed the dog, and the pan was placed under her mouth. She made no attempt to take the food, but the muscles of the head began to twitch, then those of the neck were involved, and, in about a minute, the dog was in a tonic-clonic convulsion. The jaws were wide open at first, but then closed. The convulsion lasted for three minutes, after which the dog was quiet.

The condition did not appreciably change during the next day, the respiratory rate remaining at 80 or 90 and the temperature at from 103 to 104.5 F. The dog died during the night of February 18. At autopsy, the lungs showed only slight foci of consolidation. Nothing in the appearance of the heart or other organs gave a clue as to the cause of death. Pieces of the lung, medulla and cerebellum were fixed in formaldehyde and sent to Dr. Alexander Fraser, who reported intense congestion and bronchopneumonia in the lungs and slight meningitis, with foci of encephalitis in the cerebellum and medulla.

EXPERIMENT 7 (table 5) —A male mongrel, weighing 12.5 Kg, was fed a mixture of 45 Gm of dried meat residue, 45 Gm of cracker meal, 15 Gm of bone-ash, 10 Gm of vitavose, 150 Gm of salt, 30 cc of maize oil and 500 cc of water. At 10 50 a m on April 3, a mixture of 10 cc of a pneumococcus autolysate and 10 cc of a fresh suspension, equivalent to 600 cc of an eighteen hour culture, was injected into the trachea. The temperature rose from 100.5 to 103.3 F at 12 30 p m and to 105.4 F at 1 50. It continued at this height until 4 40 p m, but by 11 50 p m, it had fallen to 104.4 F. The respiratory rate was not greatly increased, remaining at 35 or 40 all afternoon and falling to 25 at 11 50. Next morning, the temperature was 101 F and the respiratory rate was 180, but the dog was obviously sick, being scarcely able to move. At 11 a m he was dead. Autopsy showed edema of the neck near the site of injection. The trachea was clear. The chest was half filled with bloody fluid. The pericardium was adherent to the sternum. The interior of the pericardial sac was smooth. The heart was greatly dilated on the right side. There were emphysema and congestion of the lungs.

TABLE 5—*Fatal Pneumonia*

Experiment 5				Experiment 7			
Date	Nitrogen Gm	Chlorine		Date	Nitrogen Gm	Chlorine	
		Gross Gm	Net* Gm			Gross Gm	Net* Gm
2/ 9	3.46	0.425		3/31	7.14	1.02	
2/10	6.02	0.836		4/ 1	5.08	0.84	
				4/ 2	8.81	1.38	
2/11	3.90	0.419	0.371	4/ 3	5.06	2.26	2.16
2/12	6.96	0.181	0.157				
2/13	4.12	0.205					
2/14	4.29	0.168					
2/15	4.44	0.079					
2/16	2.37	0.033					
2/17	7.54	0.057					

* This calculation was obtained by deducting the chlorine content of the broth injected into the animal.

Microscopic examination by Dr. Fraser showed extreme congestion and several areas of consolidation. His diagnosis was "acute bilateral hemorrhagic bronchopneumonia and pleuritis." The liver and kidneys showed granular degeneration.

COMMENT

As can be seen from an inspection of table 3, in each of the control experiments there was a marked drop in the excretion of chlorine. This fell to one fourth or one fifth of the previous amount. Correction for the amount of chlorine in the injected broth brings the amount excreted on the first day of the experiment down to one sixth or one fifth of that in the foreperiod. Subsequently, the amount of chloride in the urine increased, so that on the fourth day of fasting, it was two-fifths or one-half as great as in the foreperiod.

These results are in marked contrast to those obtained in the experiments in which pneumococcus cultures were injected into the same dog. The excretion of chloride was not reduced on the first day,

it remained unchanged, or was slightly increased, in the two experiments (62 and 63) in which only a slight pyrexia was induced, and was more than doubled in experiment 61, in which the effect on the dog's temperature and respiratory rate was more marked. On the second and third days, there was a corresponding diminution below the level observed in the control experiments. In experiments 62 and 63, it again rose to values resembling those obtained after the injection of sterile broth. In experiment 61, in which the initial loss of chlorine was the greatest, the depletion of the body's store of chlorine was great and the amount excreted remained low. However, here also, analyses of the individual voidings of urine disclosed, after the initial sharp rise and fall, a secondary rise in the ratio of chlorine to nitrogen

TABLE 6—*Nitrogen and Chlorine Content of the Urine Obtained in Experiment 61*

Date	Nitrogen, Gm	Chlorine, Gm	100 Chlorine
			Nitrogen
February 11	2.44*	2.060	84.5
	2.48	0.504	20.3
	1.48	0.079	5.3
February 12	0.81	0.088	10.8
	1.03	0.117	11.3
	1.01	0.041	4.1
	1.78	0.046	2.6
February 13	3.00	0.045	1.5
	1.89	0.017	0.9
	2.11	0.009	0.43
February 14	6.11	0.029	0.47

* Voided at about 6 p. m. eight hours after the first injection and five or six hours after the temperature began to rise.

(table 6). Later, this again diminished, just as it does in the fasting person.²⁷

The experiment on dog 5 was unsatisfactory because some urine was retained from the first to the second day. Nevertheless, it is quite obvious, from a comparison of tables 4 and 5, that on the first day the excretion of chlorine was greater, and, on the second and third days, less than in the control experiments.

Dog 7, which succumbed to a severe pneumonitis (and septicaemia?), showed a loss of chlorine that in proportion to the body weight, was even greater than that observed in experiment 61. Not less than 2 Gm of "excess" chlorine was excreted in twenty-four hours. This is the equivalent of 0.26 Gm of sodium chloride per kilogram of body weight, or of 16 Gm of sodium chloride for a person weighing 62 Kg (136 pounds).

Unfortunately, analyses of the blood or serum were not made, but it is scarcely conceivable that all of the chloride lost should have

been in the blood, for this could have contained only 3 Gm of chlorine at the beginning of the experiment. The loss, per kilogram of body weight, was 0.16 Gm, or 4.51 milliequivalents. Assuming that the body fluids represent approximately two thirds of the body weight, and that the loss of chloride was evenly distributed, there was a diminution of 6 mg per liter. This is not so great as that frequently observed in the plasma of patients with pneumonia, but is, nevertheless, considerable.

The significance of these results would appear to be obvious. If I had been unable to collect the urine during the first few hours of experimental pneumonia in dogs, as is the case in pneumonia in man, I might well have concluded that dogs with pneumonia excrete a smaller amount of chlorine than do normal, fasting dogs and that this relative retention continues for a day or two after the crisis of the disease.

At this point, reference must be made to the work of Medigreceanu,³⁰ who, in 1911, reported the results of two experiments on the metabolism of dogs infected with pneumococci by the method of Lamar and Meltzer.²⁸ Medigreceanu concluded that "The chlorine output is very much diminished during the process of experimental pneumonia in dogs (Tables I and II). The quantity of chlorine retained in the cases with well-developed exudates (Table I) is much larger than the exudate could account for."

The interpretation of Medigreceanu's tables is not quite simple. His table I is not at all clear. It is stated that the dog took no food on the two days following insufflation. Nothing is said of the day of insufflation. If food were taken on that day, the results obtained are incomprehensible, but if it were refused, the results are more nearly in agreement with those I obtained in experiments 62 and 63. Just as in these, the excretion of chlorine remained unchanged. Medigreceanu had no control experiments, and consequently failed to obtain results such as those shown in table 3. On the five days following insufflation, the excretion of chlorine was greatly reduced, but there was no subsequent increase above the normal during the remaining three days of the experiment. The three days before insufflation showed an average daily loss of 0.025 Gm of chlorine. The following nine showed a net retention of 3.2 Gm, in spite of a loss of body weight of 0.5 Kg and of 22 Gm of nitrogen. What became of the retained chlorine is not clear. (If a ration had been taken on the day of insufflation, the amount of chloride to disappear would have been 5.6 Gm.)

³⁰ Medigreceanu, F. J. *Exper. Med.* **14**: 289, 1911.

Medigreceanu's second dog had a less marked retention. The temperature did not rise quite so high, and there was no dulness or bronchial breathing. Apparently, the dog was not very ill, for the full ration was taken daily. During the control period, the ratio, 100 chloride nitrogen, was 24.6. On the day of insufflation, it rose to 31.6. On the four following days, it was 9.2, 26.7, 28.2 and 24.6, respectively. These results seem to indicate an excess excretion of 0.58 Gm. of chlorine on the day of insufflation, followed by a retention of 1.13 Gm., accompanied by an increase in body weight, and then a loss of 0.19 and 0.14 Gm., respectively, on the two following days, as the body weight fell. The net change was an increased loss of 0.22 Gm.

Medigreceanu's experiments, therefore, cannot be accepted as contradicting the results here reported. On the contrary, the results of his second experiment are in harmony with the views expressed here.

The retention of chlorine is not peculiar to pneumonia. It has been observed in other fevers.³¹ Curiously enough, malaria is an exception in that the febrile period is characterized by an increased excretion of chlorine. But malaria is precisely the condition in which it is possible to study changes during the onset of the fever. The loss of chlorine in a short period may be considerable, as much as 8 or 10 Gm. in six hours (Traube and Jochman³² and von Limbeck³³). Moreover, according to Ringer,³⁴ Terray⁶ and von Moraczewski,⁸ the greater part of the increased excretion occurs during the development of the fever and not during its height. The chlorine content of the plasma is reduced during the febrile period, while the rate of excretion is still greater than normal, indicating a lowered threshold for chloride.³⁵

It is interesting to observe that McLean,³⁶ in 1915, concluded

Chloride retention in pneumonia is associated with a lowered concentration of chloride in the plasma, and failure of excretion is apparently due to this cause. The threshold is often considerably lowered during fever and usually returns to normal after the temperature becomes normal.

The full significance of these observations seems not to have been realized.

No observations on the retention of chlorine during the first few hours of pneumonia in man are available. Most of the records begin

31 Garratt, C. G. *Tr. Med-Chir. Soc., London* **87** 163, 1904.

32 Traube, L., and Jochman, P. *Deutsche Klin.* **7** 511, 1855.

33 Von Limbeck, R. *Wien med. Wchnschr.* **44** 2129, 2182 and 2225, 1894.

34 Ringer, S. *Tr. Med-Chir. Soc., London* **43** 361, 1859.

35 Von Koranyi, A. *Ztschr. f. klin. Med.* **34** 1, 1898. Liu, S. H. *Chinese J. Physiol.* **2** 151, 1928.

36 McLean, F. *J. Exper. Med.* **22** 36, 1915.

with the third day, or later. But, in 1880, Rohmann⁵ reported a loss of 272 Gm of chlorine on the third day and of 0.101 Gm on the fourth day in a patient who retained 8 Gm, or more, of chlorine during the following six days. Von Moraczewski⁸ observed a loss of 0.025 Gm of chlorine on the fifth day (the first day of observation) in a patient who retained about 1 Gm each day for the following six days and 0.52 and 0.38 Gm on the seventh and eighth days, respectively. It is true that von Noorden³⁷ stated that, in one of his patients, he found only 2.2 Gm of sodium chloride in the urine passed from the seventh to the thirty-first hours of the disease. This is a small amount for urine retained for twenty-four hours, but it may, nevertheless, represent a loss and not a retention. Moreover, from the results obtained in experiment 61 (table 6) and from the observations on malaria that have already been discussed, it is apparent that the initial discharge of chloride may well have been nearly, if not quite, completed by the end of the seventh hour after the patient recognized that he was ill.

However, the initial loss of chloride cannot account for all of the retention that is sometimes observed, neither does it explain the negative chlorine balances that are so frequently observed after the crisis of the disease. But, as I pointed out in the first part of this paper, it is possible that 5 or 6, or even 7 Gm, of sodium chloride should be held in the consolidated lung and that a considerably larger amount should accompany the water that is so frequently retained. The total of all three—initial loss, accumulation in the lung and solution in retained water—seems more than enough to account for the maximum retention of chloride that has, thus far, been observed.

The greatest positive balance of chloride reported in the literature seems to be that reported by Sunderman for his patient B₇. In six days, this patient retained $1,469 \pm 104$ milliequivalents of chlorine, or 86 ± 6 Gm of sodium chloride. How was this distributed? In the first place, the chloride content of the serum was increased from 5.26 to 6.32 Gm per kilogram of body weight. Assuming an increase of the same magnitude in all the body fluids and estimating these at two thirds of the body weight—59 Kg at the beginning of the observation—the result is 42.4 Gm sodium chloride. During the six days of the observation, the patient lost 56 Gm of nitrogen and incurred a caloric deficit estimated by Sunderman as 7,300 calories. I have estimated that this represents a loss of tissue of 2.75 Kg. Since the patient gained 5.56 Kg, there must have been $5.56 + 2.75 = 8.33$ Kg of water

37 Von Noorden, C. *Lehrbuch der Pathologie des Stoffwechsels für Aerzte und Studierende*, Berlin, A. Hirschwald, 1893, vol. 13, p. 222.

retained. If this is multiplied by 6.32, the concentration of sodium chloride at the end of the observations, the result is 52.4 Gm. The total of the two is 94.8 Gm. On deduction of the sodium chloride in the 2.75 Gm of catabolized tissue, or 3.4 Gm, the net total is 91.4 Gm. The observed retention was 86 ± 6 Gm.

The case just discussed was complicated by the appearance of edema and of an abnormally high concentration of chloride in the serum. The next highest retention of chloride reported by Sunderman is also one of the highest recorded in the literature, and only Sunderman's data are sufficient for a complete analysis.

In this case the concentration of chloride in the serum increased from 4.86 to 5.56 Gm per kilogram. Calculating that an increase of the same order occurred in all the tissue fluids, and that these constitute two thirds of the body weight, the result is 23.8 Gm of sodium chloride

TABLE 7—*Retention of Chloride in Pneumonia**

Sunderman's patient B7	Weight 59 Kg
Final concentration of NaCl in serum	6.32 Gm per liter
Initial concentration of NaCl in serum	5.26 Gm per liter
	<hr/> 1.06
Estimate 40 liters tissue fluid at 1.06 Gm per liter	42.4 Gm
N loss, 56 Gm	
Calorie loss, 7,800 estimate	2.75 Kg
Gain in weight	5.56
H ₂ O retained	<hr/> 8.33 Kg at 6.32 Gm per Kg
	52.4
	<hr/> 94.8
Deduct NaCl in tissue lost	
2.75 × 1.24	3.4
	<hr/> 91.4

* The observed retention was 86 ± 6 Gm. The patient gained 1,050 Gm in the first four days. The chloride rose from 90 to 99 mg or from 5.26 to 5.79 Gm.

The loss of 68 Gm of nitrogen and 4,000 calories in eight days indicates a loss of tissue of about 2.5 Kg. The actual loss in weight was only 1.76 Kg, indicating a retention of 0.74 Kg of water. This would contain 4.1 Gm of sodium chloride. The sum is 27.9 Gm. On deduction of the amount of sodium chloride in the catabolized tissue, estimated at 3.1 Gm, the net retention accounted for is 24.8 Gm. The actually observed retention was 37.5 ± 7.1 Gm. The agreement does not seem very good, but when one considers the numerous sources of error and the way in which they may all accumulate in this calculation, the divergence is not surprising.

It is therefore obvious why all attempts to find the retained chloride in the tissue were failures. The chloride was not accumulated in excess, but was retained in an effort to make good the previous losses.

Probably, these losses cannot be demonstrated in pneumonia in man, but they can and have been demonstrated in experimental pneumonia in dogs and in malaria in man

The mechanism by which this loss is produced is not evident, but a possible clue may be found in the work of Balcar, Sansum and Woodyatt³⁸ In the discussion of their results they wrote

It is proposed that in the ordinary febrile diseases, such as typhoid, tuberculosis and others, the symptom fever is due to a deficit of "free" water resulting from an abnormal tendency on the part of the colloids of the body to bind the water The poison of the disease leads to changes of the cell colloids and increases their hydration capacities, so that they take up more water

The effect of this on the "free" water of the body is thus the same as that of thirst or the introduction of salt or sugar into the body from without

TABLE 8—*Retention of Chloride in Pneumonia**

Sunderman's patient Bc		Weight 50.6 Kg
Final concentration of NaCl in serum		5.56 Gm per liter
Initial concentration of NaCl in serum		4.86 Gm per liter
		<hr/> 0.70
Estimate 34 liters tissue fluid at 0.7 Gm per liter		23.8 Gm
N loss, 68 Gm	Estimate, 2.5 Kg tissue	
Calorie loss, 4,000 Gm		
Actual loss in weight, 1.76 Kg		
0.74 Kg tissue replaced by water $\times 5.56$		<hr/> 4.1 Gm
		27.9
Deduct NaCl in tissue lost, 2.5×1.24		<hr/> 3.1
Total NaCl accounted for		<hr/> 24.8

* The observed retention was 37.5 ± 7.14 Gm

Without necessarily subscribing to the interpretation that the fever in pneumonia and malaria is due to the increased hydration of the colloids, but merely accepting the view that, in these conditions, the colloids of the plasma bind more water than they normally do, the initial outpouring of chloride is easily understood³⁹ If there is this difference

38 Balcar, J. O., Sansum, W. D., and Woodyatt, R. T. Fever and Water Reserve of the Body, *Arch. Int. Med.* **24**: 116 (July) 1919

39 It is quite possible that the increased hydration of the plasma after exposure to high temperatures (Lozinsky, E. *Am. J. Physiol.* **67**: 388, 1923-1924; Barbour, H. G., Dawson, M. H., and Neuwirth, L. *Ibid.* **74**: 204, 1925) or in cocaine fever (Barbour, H. G. *J. Pharmacol. & Exper. Therap.* **427**: 291, 1926) and the anhydremia due to cold (Barbour, H. G., and Hamilton, W. F. *Am. J. Physiol.* **73**: 385, 1925) may be due to the same effect of temperature on the capacity of the plasma proteins to combine with water. The diuresis following exposure to cold may, therefore, be caused in part, by the increased concentration of "free" water in the plasma and not, as is generally believed, entirely by the peripheral vasoconstriction.

between "free" and "combined" water, the excretion of sodium chloride would depend on its concentration in the "free" water. Diminution in the amount of the latter would lead to the increased concentration of sodium chloride therein. This would lead to an increased excretion. Thereafter, analyses of plasma or serum would show a diminished concentration of chloride, although the concentration in the "free" water might be normal, or even greater than normal. Later, as defervescence occurs, the concentration of "free" water may increase, and the patient may suffer from a lack of chloride.

The clinical significance of these observations is not altogether clear. It may be that the increased binding of water and the loss of chloride are parts of a protective mechanism. However, the fact that the greatest losses were observed in the dogs that showed the severest reactions indicates that this is not the case but that the loss is due to the toxemia or to the pyrexia. If that is so, the administration of chloride might be indicated.

On the other hand, because of the diminished amount of "free" water, a patient with fever and a chloride content of 85 milliequivalents per liter of plasma might react toward the administration of salt as would a person free from fever with a concentration of chloride in the plasma of 100 milliequivalents per liter. The reaction of the latter would depend on the ability of the kidneys to excrete the added chloride. If this were impaired, edema and circulatory disturbances might result. In a patient with pneumonia, the consequences might be serious. Again, if it were true that a concentration of 85 milliequivalents per liter of plasma is desirable in fever, a sudden return to normal temperature might find the patient with too little chloride unless some were promptly administered. Only careful trial and observation can determine under what conditions patients with pneumonia (and other fevers) should receive salt, but, in my opinion, it seems that the administration of salt is called for if the chloride content of the plasma or serum is below 90 milliequivalents per liter (0.53 Gm sodium chloride per 100 cc), and if the salt can be given without the appearance of edema. In any event, as soon as the temperature falls, an attempt should be made to restore the normal chloride content of the body fluid.⁴⁰ It is possible that some cases of postcritical collapse may be due to the sudden flooding of the body with water set free from combination with colloids, producing a too low osmotic pressure in the tissues. This might be effectively controlled by the administration of sodium chloride.

⁴⁰ R. L. Haden is the latest protagonist of the administration of salt to patients with pneumonia. A review of the literature will be found in one of his papers (*Am J M Sc* **174** 744, 1927).

SUMMARY

1 The literature on the excretion of chloride in pneumonia is briefly reviewed. This shows that the diminished excretion of chloride in the urine is not due to loss in the perspiration or in the feces and that the retention cannot be accounted for by a simultaneous retention of water, by deposition in the lungs or by an increased concentration in other tissues.

2 The symptoms following the intratracheal or intrapneumonic injection of pneumococcus cultures in dogs are described.

3 Shortly after such injection, the amount of chloride in the urine is greatly increased. This is followed by a subnormal excretion.

4 From a review of the literature it is shown that the same sequence is observed in malaria in man.

5 It is suggested that the low concentration of chloride in the plasma in pneumonia is due to a rapid excretion of chloride in the early stages of the disease. Data from the literature are shown to support this view, while none could be found to oppose it.

6 Calculation of the changes observed in the patients showing the greatest recorded retentions of chloride in pneumonia show that the retention can be satisfactorily accounted for in terms of the hypothesis here presented.

7 The clinical significance of the results is briefly discussed.

Dr. George B. Wallace extended the facilities of his laboratory to me, and my assistants, Mr. Irving Levy and Mr. Paul Brandwein, did most of the analytic work.

DISCUSSION

DR. T. S. WILDER, Philadelphia. I think that our results can be shown best by means of slides. The first slide illustrates the difference shown by two infants with lobar pneumonia, seen fairly early, the first on a high salt intake and the second on a low salt intake. In the one there was an almost immediate rapid gain in weight and then a prompt loss following the crisis. In the other there was a rapid loss in weight amounting to 3 pounds (1.4 Kg), and then an increase in weight following the crisis, after the amount of salt in the diet had been increased. This illustrates the excretion of base and chloride in the urine, showing a fairly high excretion from the first, a rise with the crisis and a reduction almost to zero at one point. One patient became extremely dehydrated while the intake of salt was low, and the other patient became edematous.

This slide illustrates the chart of the second case showing for five days a negative balance. At one point the balance was quite low. Then, following the crisis and an increase in the intake of salt, the balance became markedly positive. I should say that the second patient, the one that became dehydrated, received a large amount of water, practically 2 liters a day, and apparently could not retain the water without the salt.

This slide illustrates a case in which the intake of salt was very high. The patient retained a large amount of salt for the first few days, and then, just before death, excreted a tremendous amount, which showed that the kidneys were quite competent. The patient excreted a large excess of salt and yet retained a great deal.

The water curves in this slide show roughly that in infants on a high intake of water, 46, 71, 32 and 30 cc, the curve rose rapidly from the start, in those on a low intake, the curves dropped, in the ones on a moderate intake of about 15 cc, the weight remained high.

The question I should like to bring up is mainly this. If water is bound by the tissues, why should these infants on a very high intake of water, but receiving no salt, become dehydrated and lose weight steadily from the start?

DR J HAROLD AUSTIN, Philadelphia. I doubt the validity of Dr Greenwald's assumption that a given change of chloride concentration in the water of the serum will be associated with an equal change in the chloride concentration in the water of the whole body, since the normal chloride concentration in the water of tissue cells is only about one fifth of that in the water of serum.

Nothing in Dr Greenwald's data alters our view that it is reasonable to test clinically the program of supplying to the patient with pneumonia during the febrile period a sufficient amount of sodium chloride to permit the retention of salt appropriate to the retention of water exhibited during this period, provided the administration of salt is not pushed to the point of inducing gain in weight or edema. Clinical observation by us and by others seems to suggest benefit from such a regimen.

Dr Greenwald invokes as an explanation of the early exaggerated outpouring of chloride in his infected dogs the postulate of Balcar, Sansum and Woodyatt of increased binding of water by body colloids during the febrile state with diminution of what Woodyatt and his associates called "free water." Dr Greenwald assumes that this transfer of water from Woodyatt's "free" to "bound" state would reduce its power of holding chloride in solution. This assumption deserves examination.

Sunderman demonstrated within 2 per cent, the error of his method, that all of the water of serum is as free to dissolve chloride as is pure water, and Hill found the same to be true within 2 per cent, which was the error of his method, for the water of mammalian muscle and erythrocytes. It follows, then, that whatever may be meant by a tendency of the body colloids to bind water, there is not a particle of evidence to indicate that the power of the water to dissolve chloride will thereby be altered. Until experimental evidence is at hand that in the febrile state water is bound in serum or tissues in such a way as to alter its capacity for dissolving an electrolyte, it is not, I believe, useful to postulate such a mechanism in accounting for changes in the chloride concentration in the body.

DR GREENWALD. In reply to the observations of Dr Austin and Dr Wilder, it seems to me that both Dr Sunderman and Dr Wilder have neglected to take into consideration the fact that the tissues contain chloride, and that when these are metabolized chloride is available for excretion. If this chloride is not excreted, it is as truly retained as any chloride that is administered.

If Dr Wilder will take his figures for the nitrogen loss and look up the composition of the tissue of the human body, he will find that the chloride lost by the children who did not receive sodium chloride in the food was exactly equal to the calculated chloride content of the tissue represented by the loss of nitrogen.

In Sunderman's calculations, the body weight as a whole, including such tissues as bone, was employed. There is something wrong with his calculations. On two successive days, one person excreted 17 and 20 Gm of nitrogen, resulting in a loss of 13 and 16 Gm, respectively. The urine contained only 0.2 milliequivalent of chloride on one day and none on the other. The total chloride in the urine and feces for the two days was only 2.7 milliequivalents. A more effective retention cannot be imagined. Nevertheless, Sunderman's method of calculation made it impossible for him to determine whether there was or was not a retention.

Dr Austin has correctly pointed out that the concentration of chloride in the body fluids is only about one fifth of that in the plasma. But I am considering differences in concentration, not absolute values. If the concentration of chloride in the plasma is diminished, there must be a corresponding change in the concentration of chloride, or of some other substance capable of exerting osmotic pressure, in the tissue fluids.

It seems to me that we must assume that the disturbance of chloride metabolism in pneumonia must be the same regardless of the amount of chloride administered. The effects observed must be explained on this basis.

As to the question of bound water, the existence of bound water is purely hypothetical, but it is an attractive hypothesis. After eighty years of searching for this "retained" chloride, the existence of this bound water should not be ruled out simply because its presence has not been demonstrated. Conditions in normal defibrinated blood and in normal serum may be quite different from those in circulating plasma in patients with pneumonia.

METABOLISM IN PNEUMONIA

III THE EXCRETION OF ANIONS AND OF TOTAL BASE IN PNEUMONIA ³

ISIDOR GREENWALD, PH D

NEW YORK

The striking retention of chloride in pneumonia, which I discussed in the preceding paper,¹ long ago stimulated investigation concerning the metabolism of other inorganic constituents. Salkowski² found that the excretion of sodium was greatly diminished while that of potassium was increased. Von Moraczewski³ analyzed the urine and feces of one of his patients for potassium and sodium, and found that the retention of chlorine was accompanied by the retention of a somewhat smaller amount of sodium. There was a continued loss of potassium, which was to have been expected in view of the great loss of nitrogen which varied from 10 to 22 Gm per day.

In the same patient and in others, von Moraczewski⁴ observed a retention of calcium. This observation was confirmed by Peabody,⁵ who considered it of considerable significance. He made no control experiment and overlooked the fact that his patient received more than 2 Gm of calcium per day, and that normal persons, unless previously on a diet high in calcium, would also show a retention if fed diets containing so much calcium. The diets employed by von Moraczewski contained less calcium, and, in his experiments, negative balances were sometimes observed even when the diet contained as much as 1 Gm of calcium per day.

Von Hosslin⁶ studied the excretion of phosphorus in the urine, but he found the results to be extremely variable and came to no definite conclusion. Von Moraczewski's⁴ experiments on balance had previously shown a loss of phosphorous roughly paralleling the loss of nitrogen.

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1 Greenwald, I. Metabolism in Pneumonia. II The Mechanism of the Retention of Chloride in Pneumonia. *Arch Int Med*, this issue, p 418

2 Salkowski, E. *Virchows Arch f path Anat* **53** 209, 1871

3 von Moraczewski. *Virchows Arch f path Anat* **55** 11, 1899

4 von Moraczewski. Footnote 3, *Ztschr f klin Med* **39** 44, 1900

5 Peabody, F W. *J Exper Med* **17** 71, 1913

6 von Hosslin, H. *Deutsches Arch f klin Med* **93** 404, 1908

Austin and Sunderman⁷ analyzed specimens of urine obtained by Sunderman in his studies on chloride metabolism. They suggested that

The low chloride excretion in the precritical period of pneumonia is dependent in large measure on low chloride intake and perhaps in part upon the need for excretion of excessive amounts of sulphate, phosphate, and organic acid under the handicap of little fixed base available for excretion. It is possible, furthermore, that this demand for fixed base for excretion is a factor in the low base concentration in the serum in the precritical period of pneumonia. Correlated with this would be a tendency for lowering of the serum chloride. Furthermore, in the need for transporting the increased amounts of sulphate, organic acids, and phosphate from the tissues to the kidneys we have perhaps a reason, although not a mechanism, for the disproportionate lowering of the serum chloride.

It appears that the failure to consider the influence of the loss of body tissue led Austin and Sunderman into error.

Calculations from data given by Sunderman⁸ and by Austin and Sunderman⁷ show that the patients with pneumonia excreted the following excesses of anions over cations per gram of nitrogen lost: B_1 , 4.8 milliequivalents, B_2 , 3.55 and 3.66, B_4 , 2.2, 3.7 and 8.3, B_7 , 5.92, B_6 , 11 and 17, B_7 (eight days), 6.9, B_8 and B_9 (normal), 5 and 2.8, respectively. A similar calculation from data given by Benedict for his subject L between the twelfth and the eighteenth days of the fast, assuming that the total sulphur comprised inorganic sulphate and ethereal sulphates in such amounts as to be equivalent to 75 per cent of the total expressed as sulphuric acid, gives an indicated excess of anions over cations of 4.2 milliequivalents per gram of nitrogen. Evidently most of the values for the patients with pneumonia are normal. The few exceptions are apparently connected with a high intake of sodium chloride and may, perhaps, indicate that the retention of base is of more significance than that of chloride. However, in the absence of control experiments, no definite conclusion can be drawn.

In view of the great variation in the excretion of chlorine observed in some of the experiments described in the preceding paper, it seemed desirable to analyze the specimens of urine for other inorganic constituents. The lack of time did not permit a complete analysis of all of the specimens obtained. Those obtained in experiments 7 and 61 and in one of the control experiments were selected.

METHOD

The method of analysis employed for inorganic and ethereal sulphate was that of Folin⁹. The following method was used to determine the total phosphate and total base. The urine was oxidized with sulphuric and nitric acids. The acid

7 Austin, J. H., and Sunderman, F. W. *J. Clin. Investigation* **7** 333, 1929.

8 Sunderman, F. W. *J. Clin. Investigation* **8** 313, 1929.

9 Folin, O. *J. Biol. Chem.* **1** 131, 1905.

mixture was transferred to a platinum crucible and evaporated to dryness. The residue was dissolved in water, made slightly alkaline with ammonium hydroxide and then slightly acid with acetic acid. Ferric chloride was added until a red color was produced, and after the addition of a few drops of a 3 per cent solution of a phosphate-free hydrogen dioxide, the mixture was heated to boiling and filtered. After being washed with hot water, the precipitate was dissolved in dilute nitric acid, and the phosphorus was precipitated with molybdate solution. The precipitate was filtered on a Gooch crucible fitted with a piece of filter paper and washed with a solution containing 5 per cent ammonium nitrate and 1 per

TABLE 1—*Excretion of Anions and Total Base After the Injection of Sterile Broth, Experiment 32*

Date	Nitro gen, Gm	Chlor ine, Milli equiv a lents	Phos phate, Milli equiv a lents*	Inor ganic Sul phate, Milli equiv a lents	Etheral Sul phate, Milli equiv a lents†	Total Anions, Milli equiv a lents	Total Base, Milli equiv a lents	Excess Anions, Milli equiv a lents	Comment
March 30	15.69	55.6	32.9	39.3	1.9	129.7	24.0	105.7	
31	9.84	34.7	11.5	17.7	0.9	64.8	24.9	39.9	
April 1	10.69	22.0	24.8	31.0	1.2	79.0	16.0	63.0	
2	11.02	28.2	37.3	28.8	1.1	95.4	13.5	81.9	
3	1.06	2.76	5.46	3.0	0.09	11.31	0.05	11.26	Voided six hours after injection
	1.35	3.89	4.75	3.65	0.16	12.45	0.31	12.14	Voided six hours later
	1.94	3.72	20.0	5.96	0.40	30.08	0.00	30.08	Voided during night
Total 3	4.85	10.37	30.21	12.61	0.65	53.84	0.36	53.48	Injected broth con tained 2.57 milli equivalents chlor ine, 0.66 milliequiv alents phosphorus and 4.61 milliequiv alents total base
April 4	1.82	11.3	10.5	5.12	0.27	27.19	2.7	24.49	Injected broth con tained 1.18 milli equivalents chlor ine, 0.27 milliequiv alents phosphorus and 1.66 milliequiv alents total base
5	3.87	26.9	17.4	9.7	0.52	54.5	24.8	29.7	Injected broth con tained 1.11 milli equivalents chlor ine, 0.27 milliequiv alents phosphorus and 1.66 milliequiv alents total base
6	5.10	14.2	26.0	14.3	0.12	54.6	10.6	44.0	

* Calculated as 1.8 milliequivalents per millimol

† Calculated as 1 milliequivalent per millimol

cent nitric acid and then with alcohol. It was then titrated with a 0.1 per cent nitric acid and alkali formaldehyde being used to remove the ammonia.

The filtrate from the basic acetate precipitate was evaporated to dryness, first in glass and then in a silica dish. After removal of most of the ammonium salts by gentle heating, the residue was transferred to a platinum crucible, evaporated to dryness and ignited. The residue was dissolved in dilute hydrochloric acid, and the sulphate content was determined by precipitation with barium chloride and weighing on a Gooch crucible.

COMMENT

Table 1 shows a remarkable diminution in the excretion of total base on the first two days of the injection of sterile broth. The amount of

total base was not only less than was required to combine with the excreted chlorine, but it was actually less than the amount injected with the broth

Following the injection of the cultures (tables 2 and 3) there was a slight excess of base over that required to combine with the chlorine

TABLE 2—*Excretion of Anions and of Total Base After the Injection of Pneumococcus Culture, Experiment 61*

Date	Nitro gen, Gm	Chlor ine, Milli equiv alents	Phos phate, Milli equiv alents*	Inor ganic Sul phate, Milli equiv alents	Etheral Sul phate, Milli equiv alents†	Total Anions, Milli equiv alents	Total Base, Milli equiv alents	Excess Anions, Milli equiv alents	Comment	
February 6	8 30	25 5	20 2	19 8	0 9	66 4	24 7	41 7		
7	10 73	20 1	39 0	33 7	1 8	94 7	30 6	64 1		
8	7 75	33 0	44 7	30 8	1 4	109 9	19 5	90 4		
9	9 64	29 1	30 2	23 6	1 0	83 9	13 6	70 3		
10	11 51	30 2	26 4	27 2	1 2	85 0	12 1	72 9		
11	2 44	58 1	0 4	7 8	0 3	66 6	50 1	16 5	Voided eight hours after first injection	
	2 48	14 2	16 4	8 6	0 4	39 6	30 2	9 4	Voided during night	
	1 48	2 2	13 9	3 3	0 2	19 6	4 7	14 9	Voided next morn ing	
Total	11	6 40	74 5	30 7	19 7	0 9	125 8	85 0	40 8	Injected culture contained 2 85 milliequivalents of chlorine, 0 59 milli- equivalents of phosphorus, and 4 11 milliequiva lents of total base
February 12	0 810	2 48	0 83	1 51	0 14	5 01	3 77	1 24	Voided three hours after injection	
	1 033	3 30	0 14	1 82	0 09	5 35	5 11	0 24	Voided four hours later	
	1 016	1 16	0 20	2 84	0 07	4 27	3 81	0 46	Voided four hours later	
	1 778	1 30	0 33	3 75	0 15	5 58	5 46	0 12	Voided during night	
Total	12	4 637	8 24	1 60	9 92	0 45	20 21	18 15	2 06	Injected culture contained 0 85 milliequivalents of chlorine, 0 19 milli- equivalents of phosphorus, and 1 29 milliequiva lents of total base
February 13	3 00	1 28	5 30	6 50	0 22	13 50	2 23	11 27		
	1 89	0 48	2 19	3 77	0 45	6 58	0 78	5 80		
	2 11	0 24	5 19	6 25	0 21	11 89	2 47	9 42		
Total	13	7 00	2 00	12 88	16 52	0 56	31 97	5 48	26 48	
February 14	6 11	0 80	4 01	9 50	0 31	14 62	0 98	13 64		

* Calculated as 1 8 millicquivalents per millimol

† Calculated as 1 millicquivalent per millimol

in the urine. The excess of total anions over total cations after the injection of the cultures was not greatly different from that after the injection of sterile broth

Analysis of the individual voidings, as summarized in tables 1 and 2, shows a striking difference between the excretion of phosphorus in the first few hours after the injection of sterile broth and that after the

injection of a pneumococcus culture. In the latter case, though the length of time represented was greater by one-third and the nitrogen content of the urine was more than twice as great, the excretion of phosphorus was less than one tenth of what it was in the former.

This result is identical with that found in malaria by von Moraczewski.³ It is interesting to read his description of the sequence of the changes in the excretion of the various elements.

Wenn wir uns also nach dem Gesagten ein Schema des Fiebers entwerfen wollten, so hatte dieses folgende Gestalt. Die erste Erhöhung der Temperatur soll eine Vermehrung des Chlors (Natrium, Kalium, Calcium, Ammoniak lasse ich aus, um das Bild nicht zu complicieren), eine Verminderung des Stickstoffs (oder Vermehrung), eine Verminderung des Phosphors nach sich ziehen—Die zweite Periode, wenn das Fieber unverändert andauert, zeigt ein allmähliches Sinken der Chlorausscheidung, ein Steigen des Stickstoffs (oder Verbleiben auf der früheren Höhe) ein Sinken des Phosphors—Die dritte Periode—immer bei gleicher Temperatur—zeigt ein Sinken des Chlors, ein Steigen des Phosphors und des Stickstoffs, un zwar ist jetzt das Chlor unter Norm gesunken, Phosphor und Stickstoff über Norm gestiegen—jetzt haben wir den Ausscheidungstypus, der als Fieberharn bekannt ist. Dieses Bild kann nun andauern, wenn die Temperatur unverändert bleibt. Fallt die Temperatur (vielleicht durch Verdünnung des Blutes), so tritt das vierte Stadium ein, das Chlor wird noch mehr resiniert, der Phosphor und der Stickstoff noch mehr ausgeschieden. Dauert das Fallen der Temperatur, so erreicht Chlor das Minimum, Phosphor und Stickstoff ihr Maximum, und es ändert sich das Bild allmählich. Es tritt das fünfte Stadium ein, die Chlorausscheidung steigt bis zur Norm, Phosphor und Stickstoff kommen zur normalen Menge zurück.

(If in accordance with this we wish to outline a scheme of the fever, it would be as follows. The first increase in temperature should be followed by an increase in chlorine (I disregard the sodium, potassium, calcium and ammonia in order not to complicate the picture), an increase (or decrease) in nitrogen and a decrease in phosphorus. If the fever continues unchanged, the second period shows a gradual reduction in the elimination of chlorine, a gradual rise in the nitrogen (or a persistence at the former level) and a decrease in phosphorus. The third period—the temperature remaining the same—shows a decrease in chlorine and an increase in phosphorus and nitrogen, to be sure, the chlorine has now fallen below the normal and the phosphorus and nitrogen have increased above the normal. The type of elimination is now known as fever urine. This picture can persist only if the temperature remains unchanged. If the temperature decreases (perhaps as a result of a dilution of the blood), the fourth stage sets in: still more chlorine is retained and still more phosphorus and nitrogen are eliminated. If the fall in the temperature continues, the chlorine reaches the minimum and the phosphorus and nitrogen the maximum, and the picture changes gradually. Then the fifth stage develops in which the elimination of chlorine increases to the normal amount and the phosphorus and nitrogen have fallen to the normal quantities.)

It is amazing that von Moraczewski did not seem to realize that this initial outpouring of chlorine which he observed in malaria, may have been so largely responsible for the retention that he and others observed in pneumonia.

There can be little doubt that the initial disturbance in the metabolism of chloride and phosphate in malaria and pneumonia (and probably other fevers) is much the same. In malaria, these data are available for study, in pneumonia, they are not. A possible explanation for the initial loss of chloride is presented in the preceding paper,¹ but the mechanism by which the retention of phosphorus is brought about is still unknown.

SUMMARY

1 A review of the literature on the excretion of anions and cations in pneumonia leads to the following conclusions: (a) The increased excretion of potassium is due to the increased destruction of tissue. (b) The retention of sodium roughly parallels that of chlorine. (c) The

TABLE 3—*Excretion of Anions and Total Base After the Injection of Pneumococcus Culture, Experiment 7*

Date	Nitrogen, Gm	Chlorine, Milli equivalents	Phosphate, Milli equivalents*	Inorganic Sulphate, Milli equivalents	Ethyl Sulphate, Milli equivalents†	Total Anions, Milli equivalents	Total Base, Milli equivalents	Excess Anions, Milli equivalents	Comment
March 31	7.14	28.8	13.9	14.1	0.7	57.5	33.9	23.6	
April 1	5.08	23.7	6.1	10.3	0.4	40.5	27.2	13.3	
2	8.81	38.9	20.8	18.7	1.0	78.4	48.3	30.1	
3	5.06	63.8	29.9	12.7	0.8	107.2	65.0	42.2	Injected culture contained 2.9 milliequivalents of chlorine, 0.5 milliequivalents of phosphorus and 3.5 milliequivalents of total base.

* Calculated as 1.8 milliequivalents per millimol.

† Calculated as 1 milliequivalent per millimol.

retention of calcium reported by some observers was due to a diet high in calcium and was not related to the pneumonia. (d) There is no marked disturbance in the anion-cation balance after the pneumonia has developed.

2 The intratracheal injection of sterile broth was followed on the first day by a marked diminution in the excretion of chlorine and by an even greater decrease in the excretion of total base. The amount of the latter in the urine was less than in the injected broth.

3 During the first few hours after the injection of pneumococcus cultures, the excretion of phosphorus was much less than after the injection of sterile broth. The same diminished excretion of phosphorus during the development of the fever has previously been observed by others in malaria in man.

4 It is concluded that the initial disturbance in the metabolism of chloride and phosphorus in malaria and in pneumonia is the same.

THE SIGNIFICANCE OF CEREBROSPINAL FLUID SUGAR *

ERNEST F WAHL, M D
THOMASVILLE, GA

The purpose of this report is to add further data to that already recorded, in order to establish more definitely the relationship of the sugar in the blood and in the cerebrospinal fluid in health and disease. Although the cerebrospinal fluid has been the subject of chemical investigation for many years, it was not until an increase in the sugar in the spinal fluid was said to be diagnostic of epidemic encephalitis that quantitative determinations of sugar were given especial attention.

The amount of sugar in normal spinal fluid was at first determined by the examination of fluids promiscuously obtained. Some of these results, which were extremely variable, were undoubtedly influenced by the different methods of examination, while others were affected by the level of the blood sugar.

Shrewsbury and Williamson¹ examined 151 fluids by the Folin-Wu method. In an attempt to throw more light on the theory that glycolysis occurs rapidly, they made two readings of each of 16 fluids. Fluids examined within one hour after removal were from 1 to 8 mg higher in sugar content than when they were examined twelve hours later.

Halliday² accounted for some of the high readings of sugar in the spinal fluid by the fact that the sugar curves in the cerebrospinal fluid correspond to the sugar curves in the blood, but are delayed. He found that the amount of sugar in the spinal fluid was from 50 to 70 per cent as high as the amount of sugar in the blood when the specimens were obtained at the same time after the patients had fasted for several hours. In twenty cases of encephalitis, the amount of sugar in the blood varied from 68 to 128 mg and the amount of sugar in the spinal fluid from 42 to 70 mg.

In a comparative study of the sugar in the blood and in the spinal fluid in 206 cases of nervous and mental disease, Saye³ found the

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1 Shrewsbury, J F D, and Williamson, G F. Critical Review of the Cerebrospinal Fluid Sugar, *J Neurol & Psychopath* **9** 11 (July) 1928

2 Halliday, J L. Spinal Fluid Sugar in Encephalitis, *Quart J Med* **18** 300 (April) 1925

3 Saye, E B. Dextrose Content of Cerebrospinal Fluid in Certain Nervous and Mental Diseases, *J M A Georgia* **15** 92 (March) 1926

amount of sugar in the spinal fluid the same in psychotic as in normal patients. He considered the normal quantity to be from 40 to 60 mg.

Fremont-Smith and Dailey⁴ pointed out that blood sugar curves are followed by similar curves in the spinal fluid, so at one stage, the content of sugar in the spinal fluid might be found high after the sugar in the blood had returned to a normal level. They found sugar in the spinal fluid above 80 mg. in many conditions other than encephalitis. These instances of high sugar content in the spinal fluid are usually associated with hyperglycemia, which may be due to a metabolic disorder or to cerebral lesions. In four cases, they found an increase of from 6 to 9 mg. of sugar in the spinal fluid after an interval of from one to one and one-half hours following oral or intravenous administration of dextrose.

Greenfield and Carmichael⁵ considered the normal limits of sugar in the spinal fluid to be from 45 to 85 mg. In their experience, an increase in the sugar content of the spinal fluid is usually a reflection of an increase in the sugar content of the blood and is most likely to occur in diabetes mellitus or in nephritis, although the sugar in the spinal fluid may be slightly increased in any condition that increases the intracranial pressure. Except in these conditions, Greenfield and Carmichael do not believe that the amount of sugar in the spinal fluid ever exceeds 100 mg.

Goodwin and Sheeley⁶ are of the opinion that the sugar in the spinal fluid does not maintain a constant level in the same person and that there is no level within reasonable limits that might be considered normal for different persons. In their experience, the amount of sugar in the spinal fluid is normally, fairly constant at from 45 to 65 per cent of the amount of sugar in the blood.

Grayzel and Orent,⁷ experimenting on dogs, demonstrated the effect on the sugar in the spinal fluid of an increase in the sugar in the blood and proved the latent rise of the fluid sugar curve. Cistern punctures were made on dogs. Samples of blood and of spinal fluid were taken after the dogs had fasted and after the intraperitoneal administration of from 0.5 to 1.0 Gm. of dextrose per kilogram.

Specimens were again taken at intervals of fifteen, thirty and sixty minutes for from six to seven hours. The whole blood showed a sharp

4 Fremont-Smith, F., and Dailey, M. E. Cerebrospinal Fluid Sugar, *Arch Neurol & Psychiat* **14** 390 (Sept.) 1925.

5 Greenfield and Carmichael. *The Cerebrospinal Fluid in Clinical Diagnosis*, New York, The Macmillan Company, 1925.

6 Goodwin, G. M., and Shelley, H. J. Sugar Content of Cerebrospinal Fluid and its Relation to the Blood Sugar, *Arch Int Med* **35** 242 (Feb.) 1925.

7 Grayzel, H. G., and Orent, E. R. Blood and Cerebrospinal Fluid Sugar, *Am J Dis Child* **34** 1007 (Dec.) 1927.

rise in twenty-seven minutes and the plasma in thirty-nine minutes, while the spinal fluid reached its maximum in two hours and thirty minutes. The return to the normal level was in proportion to the rise. The whole blood reached the normal level in three hours and twenty minutes, the plasma in four hours and twenty minutes and the spinal fluid in from six to seven hours. In the animals that had fasted for ten hours, these authors found that the amount of sugar in the normal spinal fluid varied from 40 to 75 mg.

In a series of syphilitic patients, Becker⁸ found a tendency to low values of sugar in the cerebrospinal fluid when the cell count was high and the changes in the colloidal benzoin reactions occurred in the first zone. He attributed this tendency to low values to an alteration in the permeability of the meninges and of the choroid plexus by the infection. An alimentary hyperglycemia showing a blood sugar content of 185 mg per hundred cubic centimeters had no effect on the sugar in the spinal fluid, nor did five months of intensive treatment affect it.

Wilcox, Lyttle and Hearn⁹ advocated examination of the sugars in the blood and in the spinal fluid on specimens simultaneously obtained. Under such conditions, they found that the amount of sugar in the spinal fluid was from 40 to 60 per cent of the amount of sugar in the blood. Since high values occur in epidemic encephalitis, acidosis, meningitis, convulsions, nephritis and poliomyelitis of the bulbar type, this evidence cannot be considered diagnostic.

Additional evidence to support the theory that the spinal fluid is affected by the concentration of the sugar in the blood was recently furnished by Katzenelbogen.¹⁰ Experimenting with rabbits, he was able to alter both the sugar in the blood and in the spinal fluid by injections of dextrose, insulin and epinephrine. However, the meningeal permeability to dextrose varies in different, apparently healthy rabbits. It may also vary in the same rabbit from day to day without any apparent change in condition.

Penfold and Irving¹¹ recently published results that correspond more closely to the observations in this series of cases than do those of other investigators (table 1). In their series, the average amount of cerebrospinal fluid sugar was 76 mg and the lowest reading showed 68 mg.

8 Becker, S. W. The Sugar and Chloride Content of Cerebrospinal Fluid with Special Reference to Neurosyphilis, *J Lab & Clin Med* **12** 43 (Oct) 1926.

9 Wilcox, H. B., Lyttle, J. D., and Hearn, J. E. Chemical Composition of Spinal Fluid. Diagnostic Value, *Am J Dis Child* **30** 513 (Oct) 1925.

10 Katzenelbogen, S. Experimental Study on the Sugar in Blood and Cerebrospinal Fluid, *J Pharmacol & Exper Therap* **36** 231 (June) 1929.

11 Penfold, W. J., and Irving, D. H. Refractive Index of Cerebrospinal Fluid as Check on Chemical Analysis, *M J Australia* **1** 772 (June 14) 1930.

In each case reported in the accompanying tables, the blood and spinal fluid were drawn simultaneously after the patient had fasted for at least twelve hours. The readings were made within one hour after the specimens were obtained. Epstein's microchemical method on the principle of the Lewis-Benedict method was used in most instances. The

TABLE 1—*Observations of Some Investigators*

Author	Normal Spinal Fluid Sugar	Summary
Alpers, B. J., Campbell, C. J., and Prentiss, A. M. <i>Arch Neurol & Psychiat</i> 11 653 (June) 1924	50-60 mg	Average amount of spinal fluid sugar in cases of encephalitis, 82 mg, in cases of dementia praecox, 83 mg
Cookson <i>Brit M J</i> 1 157, 1925		High content of spinal fluid sugar in all cases of encephalitis in series
Crawford and Cantarow <i>Am J M Sc</i> 171 859, 1926		High content of globulin and sugar in spinal fluid characteristic of increased intracranial pressure, high spinal fluid sugar content in mental disorders
Foster and Cockrell <i>Am J M Sc</i> 167 696, 1924		Sugar content over 60 mg in 34 of 35 cases of encephalitis
Kubie and Schultz <i>J Exper Med</i> 42 565, 1925	33-51 mg	33-51 per cent of blood sugar
Levinson, A. <i>Am J Dis Child</i> 30 774 (Dec) 1925. <i>Cerebrospinal Fluid in Health and in Disease</i> , ed 2, St Louis, C. V. Mosby Co., 1923	64-106 mg	
Nixon, C. E., and Egerer Scham, G. <i>Arch Int Med</i> 25 561 (Nov) 1921	45-95% of blood sugar	
Purves Stewart, James. <i>Diagnosis of Nervous Diseases</i> , New York, E. B. Treat & Company, 1924		High content of spinal fluid sugar in encephalitis in contrast with low values in tuberculous meningitis and early poliomyelitis
Rieger, J. B. <i>Boston M & S J</i> 175 517, 1916		From 134 to 256 mg of spinal fluid sugar in cases of diabetes mellitus
Schloss, A. M. <i>Am J Dis Child</i> 11 1 (Jan) 1916	73-130 mg	
Spurling, R. G., and Maddock, C. L. <i>Arch Neurol & Psychiat</i> 14 54 (July) 1925	57-84 mg	
Stowe, W. P. <i>J Lab & Clin Med</i> 11 307, 1926	60-91 mg	"High" in two cases of encephalitis, from 10 to 15 mg in tuberculous meningitis
Thalheimer, W., and Updegraff, H. <i>Arch Neurol & Psychiat</i> 8 15 (July) 1922, <i>J A M A</i> 78 1383 (May 6) 1922	Upper limits 60-65 mg	
Wittgenstein, A. <i>Deutsche med Wchn schr</i> 49 246, 1923	45-60 mg	

readings from the Folin-Wu method did not vary materially from the microchemical readings. Readings were checked at short intervals by the Lewis-Benedict method so that fading of the standard would not affect the results.

Although a manometer was used to determine the pressure of the fluid in many of the recorded cases, the results are tabulated in the tables in other terms. In many cases punctures were made while

TABLE 2—*Encephalitis*

Race	Sex	Age, Years	Appearance of Cerebrospinal Fluid	Pressure of Cerebrospinal Fluid	Cells	Globulin	Spinal Fluid Sugar, Mg	Blood Sugar, Mg	Ratio, per Cent*	Was ser mann Reaction	Queckenstedt Reaction	Comment
W	M	42	Clear	N†	3	Neg	84	100	84	Neg	Neg	Chronic encephalitis
W	M	18	Clear	N	2	Neg	90	105	85	Neg	Neg	Chronic encephalitis
W	M	3	Clear	+4	3	Trace	80	110	72	Neg	Neg	Encephalitis following whooping cough
C	F	11	Cloudy	+2	1380	+2	80	118	67	Neg	Neg	Clinically typical acute encephalitis
			Slightly cloudy	N	450	Neg	80	120	66	Neg	Neg	
			Clear	N	16	Neg	100	128	78	Neg	Neg	Greatly improved
			Clear	N	2	Neg	84	102	82	Neg	Neg	
			Clear	N	3	Neg	86	112	76	Neg	Neg	Improving
			Clear	N	16	Neg	94	118	79	Neg	Neg	
			Clear	N	6	Neg	80	102	78	Neg	Neg	
			Clear	N	2	Neg	75	100	75	Neg	Neg	
			Cloudy	Slight increase	440	Trace	60	110	54	Neg	Neg	Acute exacerbation
			Cloudy	+1	440	Trace	80	130	61	Neg	Neg	Neutrophils 90 per cent
			Cloudy	+1	168	Trace	80	120	66	Neg	Neg	Irregular fever, stuporous
			Cloudy	N	150	Trace	90	130	69	Neg	Neg	Neutrophils 50 per cent
			Cloudy	N	88	Trace	84	112	75	Neg	Neg	Cells all lymphocytes
			Clear	N	35	Neg	90	126	70	Neg	Neg	
			Cloudy	N	11	Trace	80	98	81	Neg	Neg	Improving
			Clear	N	8	Neg	90	110	81	Neg	Neg	
			Clear	N	10	Neg	103	150	68	Neg	Neg	Improving
			Clear	N	2	Neg	92	116	79	Neg	Neg	Removed from hospital by parents
W	M	13	Clear	+4	120	Trace	80	95	84	Neg	Neg	Acute encephalitis
			Clear	+2	15	Neg	90	100	90	Neg	Neg	Complete recovery in eight days
C	M	27	Clear	N	5	Neg	115	125	90	Neg	Neg	Posten cephalitis Parkinson's syndrome
W	M	9	Clear	+4	74	+3	95	110	86	Neg	Neg	Acute encephalitis with bulbar paralysis
			Clear	+2	50	Trace	94	105	89	Neg	Neg	Bulbar symptoms disappearing
			Clear	N	28	Trace	103	101	101	Neg	Neg	Marked improvement
			Clear	N	14	Neg	100	110	90	Neg	Neg	Clinically well
			Clear	N	13	Neg	80	105	76	Neg	Neg	Apparently well twelve days after onset

TABLE 2—*Encephalitis—Continued*

Race	Sex	Age, Years	Appearance of Cerebrospinal Fluid	Pressure of Cerebrospinal Fluid	Cells	Globulin	Spinal Fluid Sugar, Mg	Blood Sugar, Mg	Ratio, per Cent*	Wassermann Reaction	Queckenstedt Reaction	Comment
W	M	5	Cloudy	+3	100	+2	118	150	78	Neg	Neg	Acute encephalitis
W	F	27	Clear	N	8	Neg	75	100	75	Neg	Neg	Chronic encephalitis
W	M	44	Clear	N	7	Neg	78	118	66	Neg	Neg	Chronic encephalitis
W	M	49	Clear	N	4	Neg	80	120	66	Neg	Neg	Chronic encephalitis
W	M	26	Clear	N	3	Neg	78	112	63	Neg	Neg	Posten cephalitic neurasthenia
W	M	26	Clear	N	1	Neg	90	118	76	Neg	Neg	Chronic encephalitis
W	M	20	Clear	N	3	Neg	90	120	75	Neg	Neg	Chronic encephalitis
W	F	32	Clear	+3	68	+1	85	100	85	Neg	Neg	Acute encephalitis
W	F	11	Clear	+4	120	+2	90	115	78	Neg	Neg	Acute encephalitis
W	M	9	Clear	+3	90	+2	85	95	89	Neg	Neg	Acute encephalitis
W	M	30	Clear	+2	110	+1	90	110	82	Neg	Neg	Acute encephalitis
W	M	22	Clear	+2	60	+1	86	108	79	Neg	Neg	Acute encephalitis
C	F	13	Cloudy	+3	220	+3	75	90	83	Neg	Neg	Acute encephalitis
Average (20 cases)							87	112	77			

* Ratio of spinal fluid sugar to blood sugar

† In this and the following tables N indicates normal

the patients were being forcibly held and it was, therefore, impossible to get them in the relaxed horizontal position that is desirable when a manometer is used. The pressure was considered normal when the fluid flowed in successive drops at a rate of more than twenty drops per minute when the stilet was first removed. When the fluid spurted in a stream from the needle, the pressure was recorded as +4. An 18 gage needle was used on adults and a 22 gage needle on infants and small children. Although this method of determining the pressure of the spinal fluid is somewhat gross, the results are satisfactory for clinical purposes.

SUMMARY

Two hundred and one readings were made on both the blood and the spinal fluid of 145 patients.

Forty-two readings in twenty cases of encephalitis gave an average of 87 mg for the sugar in the spinal fluid and 112 mg for the sugar in the blood with a ratio of 77 per cent (table 2). It is interesting to note that thirty-two readings on ten patients with acute encephalitis

gave exactly the same averages as did the readings on the entire group of patients with encephalitis. In one instance, the amount of sugar in the spinal fluid was higher than the amount of sugar in the blood. This occurred in a white boy, aged 9, when the acute symptoms were beginning to subside.

TABLE 3—*Syphilis*

Race	Sex	Age, Years	Appearance of Cerebrospinal Fluid	Pressure of Cerebrospinal Fluid	Cells	Globulin	Spinal Fluid Sugar, Mg	Blood Sugar, Mg	Ratio, per Cent*	Wassermann Reaction	Queckenstedt Reaction	Comment
C	F	25	Clear	N	2	Neg	80	108	74	Neg	Neg	Syphilitic encephalitis
W	M	60	Clear	N	1	Neg	90	100	90	Neg	Neg	Old tabes
C	M	51	Clear	N	10	Trace	82	105	78	Neg	Neg	Clinical neurosyphilis, Wassermann reaction of the blood positive, rapid improvement under treatment
W	M	62	Clear	N	3	Trace	68	80	85	+4	Neg	Neurosyphilis
W	M	40	Clear	N	11	Trace	75	100	75	+4	Neg	Tabes
W	M	59	Clear	N	9	Neg	70	106	66	+3	Neg	Tabes
W	M	51	Clear	N	40	+2	78	110	70	+4	Neg	Paresis
W	M	45	Clear	N	11	Trace	80	120	66	+	Neg	Paresis, treatment given for one year
W	F	38	Clear	N	13	Trace	76	110	69	+4	Neg	Tabes
W	F	50	Clear	N	27	+2	70	90	77	+4	Neg	Taboparesis
W	M	38	Clear	N	68	-3	90	124	72	+4	Neg	Neurosyphilis
W	F	14	Clear	N	3	Neg	80	122	65	Neg	Neg	Congenital syphilis
W	M	60	Clear	N	6	Neg	88	100	88	Neg	Neg	Periostitis of the frontal bone clinically diagnosed as neurosyphilis
W	M	42	Clear	N	52	+2	79	113	69	+4	Neg	Neurosyphilis
Average (14 cases)							79	106	74			

* Ratio of spinal fluid sugar to blood sugar

Fourteen patients with syphilis showed an average of 79 mg of sugar in the spinal fluid and of 106 mg of sugar in the blood, with a ratio of 74 per cent (table 3).

Thirty-three patients with miscellaneous neurologic lesions showed an average of 84 mg of sugar in the spinal fluid and an average of

TABLE 4—Miscellaneous Neurologic Cases

Race	Sex	Age, Years	Appearance of Cerebrospinal fluid	Pressure of Cerebrospinal fluid	Cells	Globulin	Spinal fluid Sugar, Mg	Blood Sugar, Mg	Ratio, per Cent*	Wassermann Reaction	Queckenstedt Reaction	Comment
W	M	28	Clear	N	10	Trace	90	110	81	Neg	Neg	Acute myelitis cord emulsion failed to give positive results after inoculation of rabbits and guinea-pigs
W	M	26	Clear	N	3	Neg	78	114	68	Neg	Neg	Healed myelitis with spastic paraplegia
W	M	41	Clear	N	14	Trace	90	120	75	Neg	Neg	Myelitis following exhaustion from heat
W	M	19	Clear	N	2	Neg	80	105	76	Neg	Neg	Acute malaria with symptoms of cerebral thrombosis
C	F	14	Clear	N	4	+1	100	110	90	Neg	Neg	Paramyoclonus multiplex
C	F	18	Clear	N	5	Neg	82	102	80	Neg	Neg	Bilateral cervical ribs, spastic quadriplegia
W	F	13	Clear	+3	10	+1	95	115	82	Neg	Neg	Acute uremia
W	F	15	Clear	N	1	Neg	85	110	77	Neg	Neg	Unclassified type of familial disease of central nervous system
W	M	56	Clear	N	2	Neg	80	104	77	Neg	Neg	Cerebral thrombosis
C	M	60	Clear	N	192	+1	90	120	75	Neg	Neg	The douloureux, occurring two days after injection of alcohol, neutrophils, 50 per cent
C	M	34	Clear	N	2	Neg	108	120	90	Neg	Neg	Cerebral thrombosis
C	M	49	Clear	N	2	Trace	80	110	72	Neg	Neg	Syringomyelia
W	M	22	Clear	N	2	Neg	80	101	77	Neg	Neg	Pseudobulbar paralysis
C	M	10	Clear	N	1	Neg	90	105	85	Neg	Neg	Narcolepsy
W	M	24	Slightly yellow	Decreased	8	Trace	84	102	82	Neg	Pos	Pachymeningitis
			Clear	Decreased	76	Trace	90	110	81	Neg	Pos	Recovery in six months
W	M	59	Clear	N	2	Neg	100	130	76	Neg	Neg	Paralysis agitans
W	M	59	Clear	N	4	Trace	92	112	82	Neg	Neg	Amyotrophic lateral sclerosis
W	M	49	Clear	N	10	Neg	80	115	69	Neg	Neg	Cerebral arterio sclerosis hypertrophic arthritis

* Ratio of spinal fluid sugar to blood sugar

TABLE 4—*Miscellaneous Neurologic Cases—Continued*

Race	Sex	Age, Years	Appearance of Cerebrospinal Fluid	Pressure of Cerebrospinal Fluid	Cells	Globulin	Spinal Fluid Sugar, Mg	Blood Sugar, Mg	Ratio, per Cent*	Was sermann Reaction	Queckenstedt Reaction	Comment
W	M	56	Clear	N	5	Neg	88	112	78	Neg	Neg	Old fracture of first lumbar vertebra cord injury
C	M	42	Clear	N	1	Neg	89	140	63	Neg	Neg	Pulmonary tuberculosis, parkinsonian tremor of unknown etiology
C	M	19	Clear	N	8	Neg	75	104	72	Neg	Neg	Bell's paralysis
W	M	42	Clear	N	3	Neg	65	108	78	Neg	Neg	Vertigo cause unknown
W	M	70	Clear	N	1	Neg	86	110	78	Neg	Neg	Cerebral arterio sclerosis
W	M	57	Yellow	Low	13	Trace	74	110	67	Neg	Pos	Tumor of the spinal cord
W	F	30	Clear	N	4	Neg	72	108	66	Neg	Neg	Old polio myelitis
W	M	40	Clear	N	11	Trace	74	118	62	Neg	Neg	Chronic alcoholism Korsakoff's syndrome
W	M	58	Clear	N	7	Neg	76	100	76	Neg	Neg	Pulmonary tuberculosis cerebellar tubercle
W	M	48	Clear	N	2	Neg	72	112	64	Neg	Neg	Progressive muscular atrophy
W	M	27	Clear	N	3	Neg	85	110	77	Neg	Pos	Pott's disease obstruction to iodized poppy seed oil 40% from 6th to 8th dorsal vertebra
W	M	73	Clear	N	2	Neg	90	112	80	Neg	Neg	Cerebral arterio sclerosis
W	F	59	Clear	N	47	Trace	75	105	71	Neg	Neg	Cerebral softening
			Clear	Low	40	Trace	90	110	81	Neg	Pos	
W	F	65	Clear	N	3	Neg	72	110	65	Neg	Neg	Hemiplegia
C	F	10	Clear	N	1	Neg	78	105	74	Neg	Neg	Peripheral neuritis
Average (33 cases)							84	111	75			

* Ratio of spinal fluid sugar to blood sugar

111 mg of sugar in the blood, with a ratio of 75 per cent. The highest reading for sugar in the spinal fluid in this group was 100 mg and occurred in a patient with paramyoclonus multiplex. This represented a ratio of 90 per cent (table 4).

TABLE 5—*Meningitis*

Race	Sex	Age, Years	Appearance of Cerebrospinal Fluid	Pressure of Cerebrospinal Fluid	Cells	Globulin	Spinal Fluid Sugar, Mg	Blood Sugar, Mg	Ratio, per Cent*	Wassermann Reaction	Queckenstedt Reaction	Comment
W	M	5	Cloudy	-4	2,460	+2	70	94	74	Neg	Neg	Streptococcus meningitis, spinal fluid sugar quickly dropped to zero, death in 25 days
C	I	30	Cloudy	+3	760	+2	30	106	28	Neg	Neg	Tuberculous meningitis
W	M	11	Clear	+2	388	+1	55	90	61	Neg	Neg	Tuberculous meningitis
			Cloudy	+3	1,042	+2	34	110	30	Neg	Neg	
			Cloudy	+1	983	+1	22	100	22	Neg	Neg	
			Cloudy	+1	1,486	+1	0	108	0	Neg	Neg	Death occurred
W	F	8	Cloudy	+4	1,124	+2	61	110	58	Neg	Neg	Streptococcus meningitis
			Cloudy	+2	743	+2	30	100	30	Neg	Neg	
			Cloudy	+2	974	+2	0	90	0	Neg	Neg	Died
W	M	18 mo	Cloudy	+3	2,400	+2	0	120	0	Neg	Neg	Tuberculous meningitis neutrophils, 65 per cent
			Cloudy	+3	1,100	Trace	40	120	33	Neg	Neg	Neutrophils, 40 per cent
C	F	30	Cloudy	+2	1,360	+2	30	100	30	Neg	Neg	Tuberculous meningitis
W	F	23	Yellow and cloudy	+4	1,611	+2	116	144	80	Neg	Positive affected side	Streptococcus septicaemia and meningitis, thrombosis of the left cavernous sinus
W	M	17	Clear	+2	250	Trace	82	100	82	Neg	Neg	Bilateral otitis media, mastoiditis, lobar pneumonia, pleurisy with effusion, acute nephritis, meningitis (?), no organisms recovered from fluid
			Clear	Decreased	62	Trace	90	120	75	Neg	Neg	
			Clear	Decreased	20	Neg	84	106	79	Neg	Pos	
			Slightly cloudy	Decreased	22	Trace	84	110	76	Neg	Pos	
			Clear	Decreased	12	Trace	90	110	81	Neg	Neg	Mentally clear
			Clear	N	10	Neg	82	105	78	Neg	Neg	
			Clear	N	3	Neg	96	125	76	Neg	Neg	Complete recovery after two months
W	F	36	Cloudy	+1	844	-3	10	90	11	Neg	Neg	Tuberculous meningitis
W	M	22	Cloudy	+2	560	-2	0	110	0	Neg	Neg	Tuberculous meningitis

* Ratio of spinal fluid sugar to blood sugar

TABLE 5—*Meningitis—Continued*

Race	Sex	Age, Years	Appearance of Cerebrospinal Fluid	Pressure of Cerebrospinal Fluid	Cells	Globulin	Spinal Fluid Sugar, Mg	Blood Sugar, Mg	Ratio, per Cent*	Wassermann Reaction	Queckenstedt Reaction	Comment
W	M	42	Clear	+1	68	Trace	68	112	60	Neg	Neg	Tuberculous meningitis
			Clear	N	50	Trace	66	100	66	Neg	Neg	Pott's disease
			Slightly cloudy	+1	74	Trace	60	114	52	Neg	Neg	
			Cloudy	+2	68	+1	52	110	47	Neg	Neg	
			Cloudy	+1	114	+1	42	90	46	Neg	Neg	
			Cloudy	+1	108	+1	45	108	41	Neg	Neg	
			Cloudy	Slight increase	278	+1	30	100	30	Neg	Neg	
			Cloudy	+1	580	+1	25	114	22	Neg	Neg	
			Cloudy	+1	464	+2	22	106	20	Neg	Neg	
			Cloudy	+1	320	+1	15	100	15	Neg	Neg	
			Cloudy	+1	420	+2	0	94	0	Neg	Neg	
			Cloudy	+1	540	+2	0	90	0	Neg	Neg	Died
C	F	30	Cloudy	+4	470	+2	30	114	26	Neg	Neg	Tuberculous meningitis
			Cloudy	+2	380	+1	15	100	15	Neg	Neg	
			Cloudy	+2	244	+1	15	85	17	Neg	Neg	
			Cloudy	+2	412	+1	0	110	0	Neg	Neg	
			Cloudy	+2	390	+1	0	106	0	Neg	Neg	Died
Average (12 cases)							36	105	34			

* Ratio of spinal fluid sugar to blood sugar

Thirty-nine readings were made on twelve patients with meningitis (table 5). The average amount of sugar in the spinal fluid for the group as a whole was 36 mg and the average amount of sugar in the blood was 105 mg, giving a ratio of 34 per cent. Of this group, eight patients had tuberculous meningitis, and the average quantity of sugar in the spinal fluid in these eight patients was 27 mg, which represented a ratio of 26 per cent. The remaining four cases are somewhat misleading, as some of them were not followed long enough to determine the effect of prolonged infection. The average amount of sugar in the spinal fluid in these four cases was 74 mg, which was 68 per cent of the average amount of sugar in the blood. The tendency of the sugar in the spinal fluid to decrease in tuberculous and purulent meningitis as shown in table 5 corresponds to the observations of other investigators.

The observations in multiple sclerosis and combined sclerosis are of no diagnostic significance (table 6 and 7).

Five patients with diabetes mellitus showed the effect of a high content of sugar in the blood on the sugar in the spinal fluid. However,

the relationship of the sugar in the blood and the sugar in the spinal fluid remains within normal limits (table 8)

The sugar in the spinal fluid of ten patients with nervous and mental disorders showed a slightly higher average than in many of the groups (table 9), being 88 mg and representing a ratio of 79 per cent

TABLE 6—*Multiple Sclerosis*

Race	Sex	Age, Years	Appearance of Cerebrospinal Fluid	Pressure of Cerebrospinal Fluid	Cells	Globulin	Spinal Fluid Sugar, Mg	Blood Sugar, Mg	Ratio, per Cent*	Was sermann Reaction	Queckenstedt Reaction	Comment
W	M	39	Clear	N	9	Neg	80	120	66	Neg	Neg	
W	F	24	Clear	N	8	Neg	70	110	63	Neg	Neg	
W	F	20	Clear	N	5	Neg	68	90	75	Neg	Neg	
W	M	46	Clear	N	2	Neg	95	110	86	Neg	Neg	
			Clear	N	3	Neg	85	110	77	Neg	Neg	
			Clear	N	2	Neg	80	100	80	Neg	Neg	After intravenous injection of typhoid vaccine at intervals of four days for four weeks
W	M	28	Clear	N	4	Neg	80	105	76	Neg	Neg	
W	F	19	Clear	N	5	Neg	78	100	78	Neg	Neg	
Average (6 cases)							79	106	75			

* Ratio of spinal fluid sugar to blood sugar

TABLE 7—*Combined Sclerosis*

Race	Sex	Age, Years	Appearance of Cerebrospinal Fluid	Pressure of Cerebrospinal Fluid	Cells	Globulin	Spinal Fluid Sugar, Mg	Blood Sugar, Mg	Ratio, per Cent*	Was sermann Reaction	Queckenstedt Reaction	Comment
W	M	69	Clear	N	3	Neg	70	105	66	Neg	Neg	Pernicious anemia
W	F	34	Clear	N	5	Neg	72	106	67	Neg	Neg	Sprue
W	F	35	Clear	N	3	Neg	90	103	83	Neg	Neg	Pellagra
W	M	52	Clear	N	3	Neg	80	110	72	Neg	Neg	Pellagra
W	M	49	Clear	N	6	Neg	75	100	75	Neg	Neg	Pernicious anemia
W	F	38	Clear	N	4	Neg	70	104	66	Neg	Neg	Pernicious anemia
W	M	36	Clear	N	5	Neg	80	110	72	Neg	Neg	Pellagra
Average (7 cases)							77	106	72			

* Ratio of spinal fluid sugar to blood sugar

Six patients with epilepsy also showed a tendency to high values, with an average of 88 mg of sugar in the spinal fluid and a ratio of 79 per cent (table 10)

Increased intracranial pressure as a cause of high values for sugar in the spinal fluid is not supported by the data on thirteen patients with tumor of the brain. The average amount of sugar in the spinal fluid was 84 mg and the average amount in the blood was 111 mg. The

TABLE 8—*Diabetes Mellitus*

Race	Sex	Age, Years	Appearance of Cerebrospinal Fluid	Pressure of Cerebrospinal Fluid	Cells	Globulin	Spinal Fluid Sugar, Mg	Blood Sugar, Mg	Ratio, per Cent*	Wassermann Reaction	Queckenstedt Reaction	Comment
W	F	40	Clear	N	3	Neg	275	330	83	Neg	Neg	Before treatment
C	F	54	Clear	N	1	Neg	240	300	80	Neg	Neg	Before treatment
			Clear	N	2	Neg	150	200	75	Neg	Neg	Insulin and diet
			Clear	N	1	Neg	120	170	70	Neg	Neg	
C	F	17	Clear	N	6	Neg	240	280	85	Neg	Neg	Before treatment no complications
W	M	40	Clear	N	3	Neg	80	118	67	Neg	Neg	Under control
W	M	55	Clear	N	48	+1	85	130	65	+4	Neg	Paresis diabetes
Average (5 cases)							170	218	75			

* Ratio of spinal fluid sugar to blood sugar

TABLE 9—*Nervous and Mental Group*

Race	Sex	Age, Years	Appearance of Cerebrospinal Fluid	Pressure of Cerebrospinal Fluid	Cells	Globulin	Spinal Fluid Sugar, Mg	Blood Sugar, Mg	Ratio, per Cent*	Wassermann Reaction	Queckenstedt Reaction	Comment
W	M	25	Clear	N	4	Neg	76	108	70	Neg	Neg	Dementia praecox
W	F	26	Clear	N	3	Neg	78	102	76	Neg	Neg	Hysteria
W	F	23	Clear	N	2	Neg	85	96	88	Neg	Neg	Hysteria
W	F	27	Clear	N	3	Neg	82	120	68	Neg	Neg	Hysteria
W	M	22	Clear	N	3	Neg	80	90	88	Neg	Neg	Dementia praecox
W	F	22	Clear	N	3	Neg	88	107	82	Neg	Neg	Moron
W	M	15	Clear	N	2	Neg	94	114	82	Neg	Neg	Dementia praecox
W	M	40	Clear	-2	4	Trace	100	110	90	Neg	Neg	Paranoia with basal metabolism +17 per cent
W	F	44	Clear	N	4	Neg	75	104	72	Neg	Neg	Dementia praecox morphinism
W	M	19	Clear	N	1	Neg	86	105	80	Neg	Neg	Moron
Average (10 cases)							84	106	79			

* Ratio of spinal fluid sugar to blood sugar

TABLE 10—*Epilepsy*

Race	Sex	Age, Years	Appearance of Cerebrospinal Fluid	Pressure of Cerebrospinal Fluid	Cells	Globulin	Spinal Fluid Sugar, Mg	Blood Sugar, Mg	Ratio, per Cent*	Wassermann Reaction	Queckenstedt Reaction	Comment
W	M	13	Clear	N	366	+3	80	102	78	Neg	Neg	Twenty four hours after convulsion
			Clear	N	36	Trace	85	100	85	Neg	Neg	Nine days after convulsion
W	F	18	Clear	N	6	Neg	84	102	82	Neg	Neg	No recent convulsion
W	F	16	Clear	N	1	Neg	100	110	90	Neg	Neg	Puncture not made after recent convulsion
W	F	24	Clear	N	3	Neg	88	105	83	Neg	Neg	No recent convulsion
C	F	14	Clear	+2	5	Neg	100	160	62	Neg	Neg	Puncture followed 48 hours of continuous convulsions
W	M	34	Clear	N	1	Neg	80	104	77	Neg	Neg	No recent convulsions
Average (6 cases)							88	112	79			

* Ratio of spinal fluid sugar to blood sugar

TABLE 11—*Tumor of the Brain*

Race	Sex	Age, Years	Appearance of Cerebrospinal Fluid	Pressure of Cerebrospinal Fluid	Cells	Globulin	Spinal Fluid Sugar, Mg	Blood Sugar, Mg	Ratio, per Cent*	Wassermann Reaction	Queckenstedt Reaction	Comment
W	M	23	Clear	+3	4	Neg	86	112	76	Neg	Neg	Right frontal tumor
W	F	27	Clear	N	8	Neg	75	100	75	Neg	Neg	Suspected cerebellar tumor
W	F	37	Clear	+1	47	Trace	90	108	83	Neg	Neg	Pituitary tumor
W	F	60	Clear	N	3	Neg	90	130	69	Neg	Neg	Pituitary tumor
W	M	3	Clear	+2	3	Neg	80	105	76	Neg	Neg	Cerebellar tumor
W	M	54	Clear	+1	8	Neg	78	115	67	Neg	Neg	Right frontal tumor
W	F	44	Clear	N	4	Neg	68	98	69	Neg	Neg	Right frontal tumor
W	M	43	Clear	+4	3	Neg	90	100	90	Neg	Neg	Left parietal endothe lioma
W	F	13	Clear	N	3	Neg	90	115	77	Neg	Neg	Left parietal tumor
W	F	45	Clear	+1	2	Neg	73	112	65	Neg	Neg	Tumor medulla
W	M	51	Clear	+1	8	Neg	86	100	86	Neg	Neg	Left frontal tumor
W	M	23	Clear	+3	4	Neg	86	112	76	Neg	Neg	Right frontal tumor
W	F	43	Clear	N	1	Neg	100	130	76	Neg	Neg	Ghoma in left frontal lobe
Average (13 cases)							84	111	76			

* Ratio of spinal fluid sugar to blood sugar

highest individual reading for sugar in the spinal fluid was 100 mg, but this was only 76 per cent of the amount of sugar in the blood (table 11)

Nineteen patients presenting no neurologic condition gave an average of 89 mg of sugar in the spinal fluid and a ratio of 76 per cent (table 12)

TABLE 12—Cases Presenting No Neurologic Condition

Race	Sex	Age, Years	Appearance of Cerebrospinal Fluid	Pressure of Cerebrospinal Fluid	Cells	Globulin	Spinal Fluid Sugar, Mg	Blood Sugar, Mg	Ratio, per Cent*	Wassermann Reaction	Queckenstedt Reaction	Comment
W	M	60	Clear	N	1	Neg	90	120	75	Neg	Neg	Hypertension
C	M	14	Clear	N	5	Neg	90	112	80	Neg	Neg	Appendiceal abscess
C	M	38	Clear	N	1	Neg	85	115	73	Neg	Neg	Rectal stricture
W	M	37	Clear	N	1	Neg	80	95	83	Neg	Neg	Pulmonary tuberculosis
C	F	18	Clear	N	6	Neg	120	210	57	Neg	Neg	Influenzal pneumonia
C	F	20	Clear	N	11	Trace	90	108	83	Neg	Neg	Mild hyperthyroidism
W	M	19	Clear	N	3	Neg	105	132	79	Neg	Neg	Malaria puncture not made after a chill
C	M	50	Clear	N	3	Neg	88	104	84	Neg	Neg	Essential hypertension
C	M	48	Clear	N	2	Neg	88	100	88	Neg	Neg	Chronic arthritis
C	M	38	Clear	N	2	Neg	90	118	76	Neg	Neg	Hypertension
W	M	50	Clear	N	2	Neg	88	112	78	Neg	Neg	Pellagra morphinism
W	M	40	Clear	N	2	Neg	85	130	65	Neg	Neg	Splenic anemia
C	M	41	Clear	N	2	Neg	90	104	85	Neg	Neg	Malaria and frontal headache
W	F	49	Clear	N	2	Neg	76	115	66	Neg	Neg	Myxedema
C	M	45	Clear	N	2	Neg	80	104	77	Neg	Neg	Pulmonary tuberculosis chronic alcoholism
W	M	23	Clear	N	1	Neg	85	110	77	Neg	Neg	Chronic tonsillitis, malaise headache
W	F	38	Clear	N	2	Neg	83	100	83	Neg	Neg	Myxedema with paraneoplastic background
W	F	23	Clear	N	4	Neg	80	100	80	Neg	Neg	Chronic endometritis
W	F	21	Clear	4-1	1	Neg	102	120	85	Neg	Neg	Influenza, no evidence of encephalitis
Average (19 cases)							89	116	76			

* Ratio of spinal fluid sugar to blood sugar

CONCLUSIONS

1 The ratio of the sugar in the spinal fluid to the sugar in the blood in this series of cases is higher than most of the values previously recorded. Similar results were obtained by different methods of titration.

2 A high reading for sugar in the spinal fluid is not in itself diagnostic of any given disease.

3 Table 6 shows the necessity of determining the amount of sugar in the blood simultaneously with the amount of sugar in the spinal fluid and making these readings after the patient has fasted for twelve hours.

4 In tuberculous and purulent meningitis, the sugar in the spinal fluid decreases as the disease progresses.

5 Determination of the sugar in the spinal fluid aids in the differential diagnosis of some neurologic conditions that may have similar clinical pictures, such as epidemic encephalitis and meningitis.

NATIVE COMPLEMENT IN HYPERTHYROIDISM *

N NOVICK

WASHINGTON, D C

In this communication I shall attempt to answer the question as to whether or not native complement is increased in the blood serum in hyperthyroidism, and I shall discuss the relationship between the complement value as determined by hemolytic titration and the basal metabolic rate as determined by indirect calorimetry

This study was suggested by the recent work of Hadjopoulos and Burbank¹ on the rôle of complement in health and disease. These investigators demonstrated that complement varies considerably from the normal in the course of acute infections, and that this variation is of prognostic value. They found complement increased in hyperthyroidism and decreased in hypothyroidism. "Known pathologic conditions that give rise to high metabolism such as hyperthyroidism were also found by us to give a high complement titre while the reverse was found true in true hypothyroidism." On the basis of this research, Hadjopoulos and Burbank proposed a new theory concerning the origin and nature of complement. They advanced the hypothesis that complement is a catabolic product elaborated in greater or less quantities during metabolic activity in a proportion required by the animal economy. They assumed that complement is of protein nature or a product of protein cleavage. This theory, original in its conception, is no less speculative than the various theories prevalent during the past quarter of a century, which formed the basis of sharp controversy between the German and French schools of immunology.

Metchnikoff² and his followers, principally supported by Gengou, were firmly convinced that complement (addiment) belongs to the category of cytases or soluble ferments and is an intracellular or fixed substance of the leukocytes (phagocytes). On the basis of their researches, Metchnikoff stated that complement is not free in the circulating blood, but that its presence in the serum of mammalian blood *in vitro* is due unquestionably to grave injury or destruction of the leukocytes produced during the withdrawal and subsequent clotting of the blood. He, therefore, denied the presence of free complement in the circulating blood.

* Submitted for publication, Dec 16, 1930

~ From the Laboratories of the Diagnostic Center, U S Veterans Hospital, Washington, D C

1 Hadjopoulos, L G, and Burbank, R J *Lab & Clin Med* **14** 131 (Nov) 1928

2 Metchnikoff, Eli *Natural Immunity in Infective Disease*, translated by Francis G Binni, London, Cambridge University Press, 1905

Buchner,³ theoretically agreeing that alexin is of leukocytic origin and in the nature of a ferment, held that complement is a leukocytic secretion. This contention brings up the possibility that complement is free in the circulating blood.

Ehrlich⁴ maintained, contrary to Metchnikoff's contention, that complement is free in the circulating blood and not dependent on leukocytic destruction for its presence in the serum, also that several complements, or what is spoken of as multiplicity of complement, exist.

Gurd⁵ expressed the belief that complement does not exist in the blood as such but in the form of a complementogen, and that it is activated by some substance in the leukocytes.

Zinsser⁶ conceded the fact that injury to the cells may be a factor in the production of complement, but he stated the belief that complement is free in the circulating blood. He said "Considering the very probable participation of alexine in opsonic functions, this (injection of bacteria into a living animal and finding a very rapid and active phagocytosis) would seem to point very strongly towards the presence of this substance in the circulating blood."

Kolmer⁷ expressed the opinion that complement resides in the globulin fraction of the serum protein or perhaps is carried along with the former, and that it is probably enzymic in nature.

Hyde⁸ has recently, by ingenious experiments on the frog, thrown some doubt on the contention that complement is intraleukocytic and bound. He inoculated copiously washed sheep cells intrapericardially into the frog, and for several hours made microscopic observations of the integrity and movement of these cells. During this period they were intact and uninjured. When rabbit sensitizer (amboceptor) was subsequently injected into the frog, the sheep cells were hemolyzed and could not be seen in the circulation. Hyde thought that this was an *in vivo* experiment conceding the possibility of leukocytic injury during the process of intrapericardial injection.

Hyde⁹ has also shown by his work on the plasma of a hemophiliac that the complementary property of this plasma is as potent as that of the serum obtained after retarded clotting, and that its potency is comparable to that of normally clotted blood serum. He expressed the

3 Buchner, quoted by Metchnikoff (footnote 2, p. 189)

4 Ehrlich, P., quoted by Metchnikoff (footnote 2, p. 297)

5 Gurd, quoted by Hyde, Roscoe R. (reference 8)

6 Zinsser, Hans. *Infection and Resistance*, ed. 3, New York, The Macmillan Company, 1923

7 Kolmer, John F. *Serum Diagnosis by Complement Fixation*, Philadelphia, Lea & Febiger, 1928

8 Hyde, Roscoe R. *The Complementing Properties of Blood Plasma*, *Am J Hyg* 8:859 (Nov.) 1928

9 Hyde, Roscoe R. *The Complement Deficient Guinea-Pig*, *Am J Hyg* 7:619, 1927

belief that this plasma is as nearly natural as is obtainable and quite different from artificial plasma

D'Herelle¹⁰ took an extreme view regarding the entity of complement, a view perhaps not altogether fantastic. Complement itself "is an artificial principle, a product of the laboratory."

The foregoing brief review cites the fundamental controversial points regarding the mysterious origin and nature of complement. In this study it was not my object to solve the problem of the origin of complement, rather it was hoped that the determination of an increase of complement in the blood serum in hyperthyroidism would be of practical diagnostic importance and would supplement the evidence obtained through the basal metabolic rate.

It was necessary to assemble a group of normal controls in whom enlargement of the thyroid gland was not suspected and in whom the

TABLE 1—*Grouping of Cases Selected for Study*

Normal controls	80
Normal controls (basal metabolic rate within normal limits)	30
Hyperthyroidism (unclassified)	31
Miscellaneous pathologic conditions	30
The latter group is made up as follows	
Diabetes mellitus (uncomplicated mild type)	10
Pulmonary tuberculosis	8
Neurosyphilis	7
Nephritis (chemical analysis of the blood: nonprotein nitrogen 66, urea nitrogen 35, uric acid 7.2 mg)	1
Secondary anemia (red cells, 2,400,000, hemoglobin 22%)	1
Myelogenous leukemia (white cells 175,000 and 179,000)	1
Acute arthritis and diabetes (blood sugar, 200 mg, carbon dioxide, 22% by volume)	1
Huntington's chorea	1
Total cases	171
Total determinations (titrations)	262

basal metabolic rate was within normal limits. It was equally necessary to study the variation in the titer of the hemolytic complement of normal subjects during consecutive daily periods. Additional controls on pathologic and well defined diseases were included.

In table 1 is shown the grouping of cases selected for this study. It includes a group of cases of miscellaneous diseases, citing laboratory observations that appeared pertinent to the study. One case of myelogenous leukemia is included in which the white blood cell counts at the time complement was determined are given.

The so-called average normal titer of complement in human serum is not a fixed quantity that would hold good and be reliable for comparative studies in the hands of every investigator. It depends primarily on the strength of the sheep cell suspension, used as the hemolytic indicator, and on the period of incubation. It also depends on the method of carrying out the titration, whether it is direct or whether diluted serum is used. The terminology for expressing the titer also

¹⁰ d'Herelle, F. *Immunity in Natural Infectious Diseases*, English ed by George H. Smith, Baltimore, Williams & Wilkins Company, 1924.

varies That complement is variable in the serum of different animal species is well known, not only is it variable in different species of animals, but it varies in different animals of the same species The cause of the variability of complement is not known It is commonly assumed that diet plays a considerable rôle in the potency of, for instance, guinea-pig complement

Regarding the variation of complement in human serum, in 700 specimens of blood from hospital patients, Hyde³ found the average titer to be about 30 units In only 1 per cent of his cases was the complement titer as high as 80 units, while in 2 per cent of the cases complement was not demonstrable Hadjopoulos and Buibank¹ stated that in 2,000 cases studied by them, the average normal titer was found to be 0.04 cc of active serum My study confirms the observations of Hyde in that extremely high and extremely low titers for the complement of human serum were infrequent

METHOD

An antish sheep rabbit hemolytic serum was used, and since human complement was the quantitative factor sought, the amboceptor was adjusted against a pooled human serum (from five normal persons), an arbitrary 10 per cent dilution being used The unit of the amboceptor thus determined was doubled and used as a constant in subsequent test titrations During the progress of this work, approximately seven months, the amboceptor was kept in the icebox at about 8 C and was occasionally checked The sheep cell suspension used was 2.5 per cent, freshly prepared, washed and sensitized for ten minutes at the same icebox temperature The serum tested for complement was carefully pipetted with a certified pipet into a series of tubes in graded amounts, beginning with 0.005 cc and increasing to 0.05 cc or a lower dilution was used if required Physiologic solution of sodium chloride was added to each tube, bringing the volume to 0.6 cc This was followed by incubation in a water bath at 37.5 C for five minutes Subsequently 0.4 cc of a sensitized sheep cell mixture, consisting of equal volumes of the 2.5 per cent sheep cell suspension and 2 units of amboceptor, was added, and a final incubation for fifteen minutes in a water bath at 37.5 C was allowed The entire volume in each tube was 1 cc, and the final strength of the sheep cell suspension, 0.5 per cent The results were read immediately after the period of incubation, and the tube containing the least amount of serum showing complete hemolysis was recorded as the titer of that serum The tube showing almost complete hemolysis was recorded as 3+ The absorption of native amboceptor, while desirable, was not resorted to, since for comparative studies, this factor did not appear to be of great significance The serums, with the exception of a few controls, were obtained at 2.30 p. m., kept at room temperature for one and a half hours, the clot being allowed to retract, and subsequently placed in the icebox until the next afternoon When the serums were tested they were approximately twenty-four hours old, during which period they had been kept in contact with the clot

RESULTS

The accompanying charts are graphic reproductions of the complement titer as recorded immediately after the fifteen minutes of incuba-

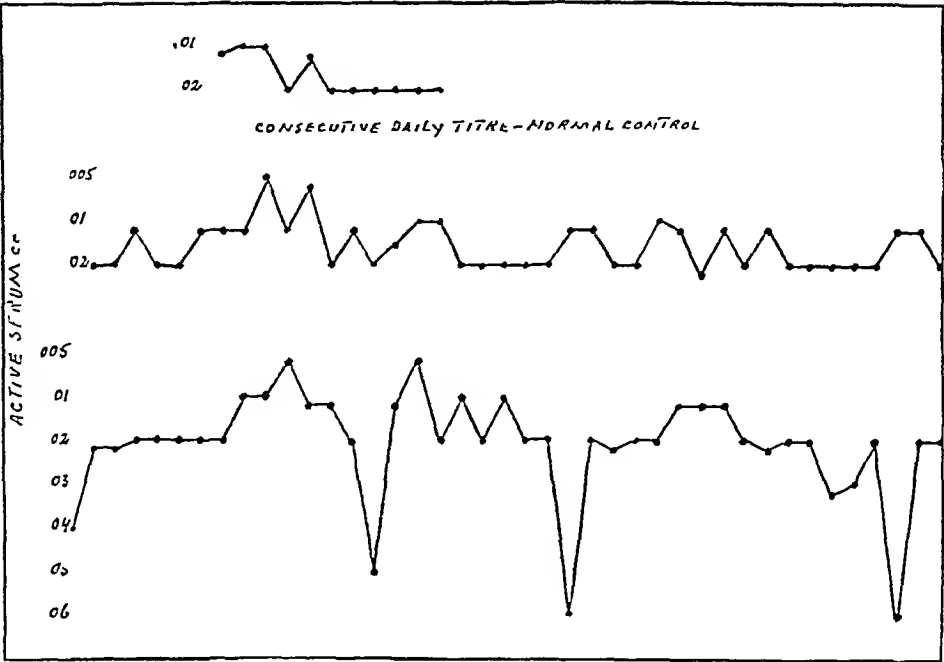


Chart 1—Graph of the complement titer in normal controls

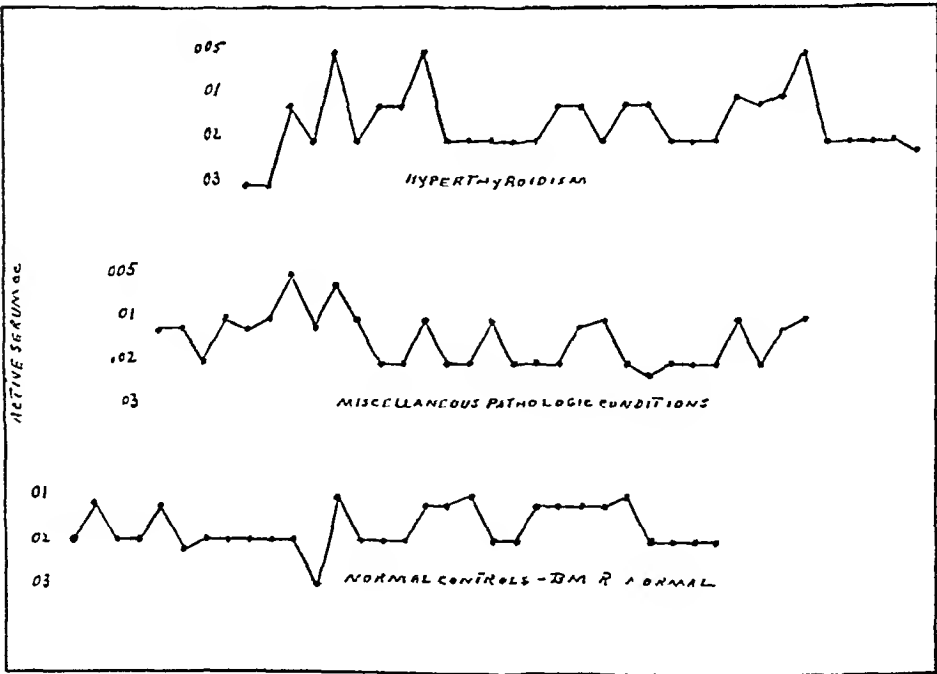


Chart 2—Graph of the complement titer in normal controls and in patients with disease

tion in the water bath at 37.5 C. A glance at the charts shows that there is a general topographic similarity in the curves. It is seen that the predominating complement titer in every group of cases is 0.02 cc of active serum, that the next most frequent titer is 0.01 cc or twice as high, and that a high titer of 0.005 cc is extremely infrequent both in the general control group and in the control group in which the basal metabolic rate was normal. A low complement titer, such as 0.06 cc, or one three times as weak, is also infrequent.

In translating the charts into figures, it is noted that in the general normal control group of eighty cases, the range of 0.02 and nearly 0.02 cc of active serum titer is furnished by forty-three cases, or 53 per cent, twenty-seven cases, or 33 per cent, fall into the range of 0.01 and nearly 0.01 cc of active serum titer. A high titer of 0.005 cc is given in four cases, or 5 per cent, and a very low titer in two cases, or 2.5 per cent. An approximately similar percentage of distribution of complement titer is seen in the normal control group in which the basal metabolic rate was within normal limits, namely, eighteen cases, or 60 per cent, furnished a titer of 0.02, and eleven cases, or 36 per cent, furnished a complement titer of 0.01 and nearly 0.01 cc of active serum. No high titer was found in this group.

Comparing the titer of the controls with that of the group of thirty-one cases with hyperthyroidism it is found that sixteen cases, or 52 per cent, showed a titer of 0.02 cc, and that in ten cases, or 32 per cent, the complement titer was 0.01 cc of active serum. Three cases of this group, or about 10 per cent, showed a high complement titer of 0.005, while two cases of the same group, or 6 per cent, furnished a titer of 0.03 cc.

It is thus seen that the incidence of variation in titer of the group with hyperthyroidism is strikingly similar to that of the normal control group. The incidence of a high complement titer associated with the typical basal metabolic rate is found in three cases, or about 10 per cent, as against four cases, or 5 per cent, in the control group. It should be noted that in two of the three cases in the group with hyperthyroidism showing a high titer, the basal metabolic rate was also high (from +41 to +42). However, in the face of the evidence presented, it would seem possible that the simultaneous high complement titer with a high basal metabolic rate in the two cases noted might be considered a mere coincidence.

Reference to chart 2 (center figure), based on thirty cases of miscellaneous pathologic conditions, shows that fourteen cases, or 46 per cent, showed a complement titer of 0.01 and that a similar number furnished a titer of 0.02 cc of active serum. Two cases of this group showed a high titer of 0.005, the highest titer recorded. It should be explained that the frequency of higher titer in this group is accounted

for by the group of diabetic patients included in it. This observation (higher titer in diabetes) is perhaps worthy of further investigation.

While it is fairly evident that, as a constant observation, an unusually high complement titer or a deviation in titer from the so-called average normal is not demonstrable in the serum of persons with hyperthyroidism, either as compared with normal controls or with patients having miscellaneous pathologic conditions, it was deemed essential, for conclusive evidence, to study the postoperative complement titer in hyperthyroidism and to compare it with the titer obtained in the same persons before thyroidectomy.

In table 2 are shown the preoperative and postoperative basal metabolic rates and the complement titer in nineteen cases. Analysis is possible in only eleven cases in which both the hemolytic titer and the

TABLE 2—*Complement Titer and Basal Metabolic Rate Before and After Thyroidectomy*

Case	Preoperative		Postoperative		
	Basal Metabolic Rate Plus	Complement Titer Ce	Basal Metabolic Rate	Complement Titer, Ce	Blood Collected After Operation Days
2	18	0.02*	+12	0.01	35
31	41	0.005*	+47	0.02	28
35	67	0.03	—7	0.01	35
4	60		—10	0.01*	50
109	38	0.02	—5	0.02	14
79	63	0.02	—5	0.02	14
93			+5	0.02	21
33	57		—5	0.02	21
101	11		+3	0.02	21
62	42	0.005*	+10	0.01*	
2	47		0	0.01*	21
73	14	0.02	+2	0.02	14
201	19	0.02	+1	0.01*	14
167	18	0.01*	+7	0.005*	7
159	15	0.02	—10	0.02*	14
192	46	0.01*	+1	0.01*	9
235	34	0.01*		0.01	4
243	45	0.02			
189	34			0.01	7

* Nearly complete hemolysis

basal metabolic rate are available. In the last column of the table, the period of postoperative collection of specimens is noted in seventeen cases. Two possible analyses are indicated. 1. The comparison of the postoperative titer of all the cases in this group except one with the larger group of cases of hyperthyroidism, the complement titer of which has already been compared with that of the normal controls. This analysis shows that approximately 50 per cent of the cases fall in the range of 0.02 cc active serum—a percentage incidence not dissimilar either to the group with hyperthyroidism as a whole or to the general normal group. 2. The comparison of the preoperative and postoperative titer with relation to the basal metabolic rate. This analysis is possible in only eleven cases, from which it is seen that while in all the cases the basal metabolic rate has returned to normal following thyroidectomy,

no change in complement titer is noted in six cases, or approximately 55 per cent, while a higher titer is noted in four cases, or 36 per cent. A single exception is noted in case 31, in which the complement titer dropped from nearly 0.005 to 0.02. The basal metabolic rate in this case did not return to normal (this patient suffered from a bilateral goiter). No significance is noted in regard to the period of collection of the sample, ranging from four to fifty days after thyroidectomy.

From the data presented in table 2 it becomes increasingly difficult to associate the complement value in the blood serum in hyperthyroidism with the basal metabolic rate.

SUMMARY

This study was undertaken to ascertain the possibility of using the native complement value in the serum of patients with hyperthyroidism as a supplementary test in the diagnosis of hyperthyroidism. It was hoped that the adoption of such a laboratory procedure would rest on the determination of an increase in the complement titer of persons with hyperthyroidism and on its relation to the basal metabolic rate. In all, 110 controls were used, in 30 of whom the basal metabolic rate was normal, and in 80 of whom the basal metabolic rate was not suspected to have been abnormal.

CONCLUSIONS

The complement titer in normal controls, in the determination of which an antish sheep rabbit hemolytic serum, a 2.5 per cent sensitized sheep cell suspension and incubation in the water bath at 37.5 C. for fifteen minutes were employed, was found to be 0.02 cc. of active serum in about 50 per cent of the cases. A titer of 0.01 is next in frequency in about 35 per cent of the cases. A high complement titer as well as a very low titer is infrequent.

No increase of complement value or significant deviation from the average normal range was found in a group of thirty-one unclassified cases of hyperthyroidism. A high titer (0.005) was found in three cases or 10 per cent, in two of which the basal metabolic rate was also high, which appears to be a mere coincidence.

The postoperative and preoperative complement value in the serum of patients with hyperthyroidism when compared with the postoperative and preoperative basal metabolic rates does not suggest any significant relationship. No change in titer was noted in 55 per cent of the cases, while a higher complement value was obtained in 36 per cent of the cases following thyroidectomy.

THE RESPIRATORY QUOTIENT

ITS USE IN THE DIAGNOSIS OF DIABETES MELLITUS

MAX WISHNOFSKY, M D

AND

CHARLES S BYRON, M D

BROOKLYN

This article is best prefaced by the following excerpt from Joslin's book, "Treatment of Diabetes Mellitus"¹

It is convenient to classify patients with glycosuria or with a history of glycosuria into four groups true diabetics, potential diabetics, renal glycosurics, and unclassified diabetics Under true diabetics are placed patients whose blood sugar on an unrestricted diet is 0.14 per cent or more fasting, or 0.17 per cent or more after a meal with simultaneous glycosuria which is plainly related to diet Potential diabetics are those with glycosuria closely related to the diet who easily become sugar-free with slight restrictions, but whose blood sugar is below 0.14 per cent fasting and never reaches 0.17 per cent after a meal Renal glycosurics are individuals who have shown a constant glycosuria, irrespective of diet, for years, are symptomless, and have a blood sugar which is invariably normal

Unclassified" diabetics by my nomenclature include the remaining cases of glycosuria, especially those associated with organic disease for example, that of the gall-bladder, kidney, occasionally of the thyroid, cancer of the pancreas and often pregnancy

In diabetes mellitus there is a disturbance in the metabolism of proteins and fats, as well as in that of carbohydrates, but from the standpoint of diagnosis it is sufficient to consider the metabolism of carbohydrates This may be studied from the following standpoints (1) the determination of the presence of glycosuria, (2) changes in the concentration of sugar in the blood, and (3) changes in the respiratory quotient These points will be considered in the foregoing order The first two will be studied cursorily and only in their relation to the main subject

Diabetes mellitus means the passing through of sugar or glycosuria It has been shown by John² and by others that the renal threshold for dextrose varies from 0.045 to 0.348 per cent of the sugar in the

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From the Departments of Metabolism and Pathology, and the Diabetic Clinic of the Jewish Hospital

1 Joslin, E P The Treatment of Diabetes Mellitus, ed 4, Philadelphia, Lea & Febiger, 1928, p 99

2 John H I Differential Diagnosis of Diabetes by Means of Glucose Tolerance, J A M A 79 1234 (Oct 7) 1922

blood It is evident that a person with a low renal threshold may have marked glycosuria, this occurs in the cases of so-called renal glycosuria or diabetes innocus It has also been convincingly shown by John² that, because the glycosuria is slight and transient, the presence of diabetes may remain unrecognized for a long time in persons with a high renal threshold and a moderately severe diabetes Glycosuria may also occur when hyperglycemia is produced by conditions other than diabetes mellitus, such as nephritis, hyperthyroidism and hypertension From the scientific standpoint the presence or absence of glycosuria is unimportant in the diagnosis of diabetes mellitus The term "diabetes mellitus" is a misnomer and does not adequately describe the condition that is known by that name The disease may more properly be termed hypo-insulinism It parallels such terms as hypothyroidism and hypopituitarism

An elevated fasting level for sugar in the blood indicates, in the vast majority of instances, the presence of diabetes mellitus However, a high content of sugar in the blood may occur in other conditions, such as hyperthyroidism, nephritis and hypertension Furthermore, as a result of restriction in carbohydrates in the diet of patients with diabetes mellitus, the sugar in the blood may be normal when the patient is fasting

Valuable information may be obtained by studying the blood sugar curve after the ingestion of dextrose, this is the dextrose tolerance test A normal blood sugar curve may be considered as one that (1) has a fasting level of from 0.7 to 1.1 Gm per liter, (2) reaches its peak in one hour after the ingestion of dextrose (usually it reaches the peak earlier and rarely goes higher than 1.7 Gm) and (3) tends to reach its fasting level within two hours occasionally in three In any case in which the curve is higher than normal, the possible presence of diabetes mellitus must be considered It has been definitely established that a high blood sugar curve may occur in the following conditions hypertension, nephritis, pregnancy, hyperthyroidism, hepatic disease and arthritis As previously stated, Joslin described these as cases of "unclassified" diabetes It appears to us that they may be more correctly called cases of unclassified hyperglycemia or glycosuria This entire subject was clearly reviewed by Ohler³

In a series of 160 cases who underwent glucose tolerance tests, glycosuria was absent with 103 and 57 showed only small amounts Of the 103 cases without glycosuria, 37 gave normal glycemic reactions, 53 definitely abnormal, and 12 doubtful reactions or in other words, 60 per cent of the cases without glycosuria gave abnormal sugar tolerance reactions An analysis of the cases in this group shows that a very large percentage of the abnormal reactions were found in the

3 Ohler, W. R., quoted by Joslin (footnote 1, p. 212)

following pathological conditions (arranged in the order of frequency) gall-bladder disease, cirrhosis of the liver, bronchial asthma, arteriosclerosis, carcinoma, obesity, endocrine disturbance, chronic nephritis, chronic arthritis

Of the 57 cases in which glycosuria was found, 9 gave perfectly normal reactions. These 9 fulfil all the requirements of so-called renal glycosuria. The remaining 48, or 84 per cent, showed definitely normal reactions, despite the fact that in every instance the fasting blood sugar was perfectly normal.

There exists, then, a group of cases, in which the foregoing method of procedure, namely, the use of the dextrose tolerance test, is inadequate in the determination of the absence or presence of diabetes mellitus.

THE CLASSIFICATION OF "UNDETERMINED" CASES

We come now to the consideration of the respiratory quotient and its use in classifying these "undetermined" cases.

The respiratory quotient of normal persons twelve hours after a meal was determined by Benedict, Emmes, Roth and Smith⁴ and was found to be 0.83 for men and 0.81 for women. As a rule it is lower in persons with diabetes, the more severe the diabetes, the lower is the respiratory quotient. The respiratory quotient during fasting is lower in normal persons if they have been deprived of carbohydrate for several days. Conversely it was shown by Benedict, Emmes and Riche⁵ that after an evening meal rich in carbohydrate, the respiratory quotient on the following day may be 0.88. It is seldom, however, that such great changes are encountered in the diet as were employed by these experimenters with their subjects. It has been shown by Bernstein and Falta⁶ and others that the respiratory quotient after the administration of dextrose will not rise until an optimum percentage of glycogen in the liver is obtained. It is only after the glycogen depots have been filled that the oxidation of dextrose will commence. Consequently, in a person who has been on a diet poor in carbohydrate for several days, there will be a delay in the rise of the respiratory quotient, whereas when the body is surfeited with glycogen there will be an early rise, which to some extent must be attributed to the conversion of carbohydrate to fat. Gigon⁷ found that in a normal person the respiratory quotient never rises before one-half hour after the

⁴ Benedict, F. G., Emmes, L. E., Roth, P., and Smith, H. M. The Basal, Gaseous Metabolism of Normal Men and Women, *J. Biol. Chem.* **18**, 139, 1914.

⁵ Benedict, F. G., Emmes, L. E., and Riche, J. A. The Influence of the Preceding Diet on the Respiratory Quotient After Active Digestion Has Ceased, *Am. J. Physiol.* **27**, 383, 1911.

⁶ Bernstein, S., and Falta, W. Respiratorischer Stoffwechsel und Blutzuckeregulation. *Deutsches Arch. f. klin. Med.* **125**, 233, 1918.

⁷ Gigon, quoted by Bornstein and Holm (footnote 8).

administration of dextrose. Indeed, Bornstein and Holm⁸ found that the respiratory quotient may actually fall during the first fifteen minutes and suggested that this may be due to the retention of carbon dioxide in the body for the purpose of combining with alkali released by the secretion of acid in the gastric juice.

In diabetes mellitus there is a deficiency in glycogenesis and in the storage of glycogen. The question whether there is also a diminution in the ability to oxidize dextrose is still in a polemic state. Macleod⁹ stated: "The occurrence of these low quotients and their failure to respond to ingestion of glucose are often cited as evidence that the tissues in diabetes have lost the power to oxidize carbohydrates but there is no direct evidence that this is really so." Joslin¹⁰ expressed the belief that the person with diabetes can burn sugar if the sugar can first be transformed into glycogen. But since a fundamental feature of diabetes mellitus is the inability to form glycogen, then indirectly there is a diminution in the oxidation of dextrose. This may be accepted as incontrovertible. In diabetes mellitus the respiratory quotient during fasting is lower than the normal quotient, and the respiratory quotient curve fails to rise to a normal level after the ingestion of dextrose. A low respiratory quotient curve indicates a deficiency of insulin or the neutralization or inactivation of an adequate supply of insulin.¹¹ The converse is true, namely, that a normal respiratory quotient curve indicates an adequate supply of insulin.

The question to be considered now is: What constitutes a normal respiratory quotient curve? It is to be deplored that so little work has been done to put this subject on a firm basis. It is fallacious to take as a standard the amount of dextrose oxidized in a certain period, even if calculated per square meter of surface area, for the reason that the amount of active tissue in the body cannot be determined. The important feature is this: When suddenly flooded with dextrose, the normal body will oxidize it in preference to fat. The figure determined for the respiratory quotient during fasting is unimportant. The

8 Bornstein, A., and Holm, K. Ueber den respiratorischen Stoffwechsel bei alimentärer Glykämie, *Biochem Ztschr* **130** 209, 1922.

9 Macleod, J. J. R. *Physiology and Biochemistry in Modern Medicine*, ed 6, St. Louis, C. V. Mosby Company, 1930, p. 912.

10 Joslin, E. P. (footnote 1, p. 103).

11 This does not include phlorizin diabetes in which the respiratory quotient rises only slightly after the administration of dextrose. This is the result, not of the inability of the organism to oxidize dextrose, but of the rapid elimination of dextrose by the kidney. It is conceivable that in renal glycosuria if the threshold is markedly low and the excretion of dextrose extremely high, the respiratory quotient might fail to rise to the normal level after the administration of dextrose. To our knowledge no such case has been reported.

important point is What is the ratio of the amount of fat to the amount of carbohydrate oxidized two or three hours after the ingestion of dextrose? Rabinowitch¹² stated that a rise of 0.12 in the respiratory quotient may be considered normal. This is the average for a group of cases, but cannot be applied to an individual case. If the respiratory quotient during fasting is 0.71, a rise to 0.83 cannot be considered normal. It goes without saying that during fasting a rise in the respiratory quotient from 0.84 to 0.90 cannot be called abnormal. From our own observations and from those of Sanger and Hun¹³ and Bornstein and Holm,⁸ we have come to the conclusion that the respiratory quotient must rise to 0.88 within two and one-half hours in order to be considered normal.¹⁴

It was previously stated that if a high blood sugar curve is present, the presence of diabetes mellitus must be suspected. This dilemma

TABLE 1—*Curves of Respiratory Quotient in Normal Controls (Sanger and Hun)*

	Respiratory Quotient	30 Minutes*	60 Minutes	90 Minutes	120 Minutes	150 Minutes	Range
C. L.	0.78	0.82	0.80	0.89	0.87	0.94	0.16
H. D.	0.83	0.81	0.80	0.88	0.88	0.90	0.09
W. U. G.	0.75	0.84	0.88	0.88	0.84	0.90	0.15
E. H.	0.77	0.80	0.80	0.90	0.92	0.90	0.15
B. S.	0.78	0.80	0.84	0.86	0.88	0.86	0.10
M. C.	0.79	0.82	0.88	0.89	0.92	0.93	0.14
M. C.	0.83	0.83	0.86	0.83	0.92	0.90	0.09
H. J.	0.85	0.83	0.84	0.88	0.93	0.89	0.10
R. Me.	0.83	0.88	0.84	0.83	0.93	0.92	0.10
H. R. Q.	0.75	0.79	0.81	0.86	0.83	0.87	0.12
Average	0.80						0.12

* 1.75 Gm. of dextrose per kilogram of body weight

occurs particularly in cases of hyperthyroidism, hypertension and other conditions already mentioned. It was shown by Sanger and Hun¹³ that the respiratory quotient curve is normal in hyperthyroidism. Similar observations have been made by us¹⁵ in hypertension and by Linder, Hiller and Van Slyke¹⁶ in nephritis. If diabetes mellitus complicates these conditions, it will make itself evident by a low respiratory quotient curve.

12 Rabinowitch, I. M. Simultaneous Respiratory Exchange and Blood Sugar Time Curves Obtained in Diabetic and Non-Diabetic Individuals Following Ingestion of Glucose, *J. Clin. Investigation* **2** 143, 1925.

13 Sanger, B. J., and Hun, E. G. The Glucose Mobilization Rate in Hyperthyroidism, *Arch. Int. Med.* **30** 397 (Sept.) 1922.

14 Sanger and Hun, as well as we, employed 1.75 Gm. of dextrose per kilogram of body weight. Bornstein and Holm gave 100 Gm. per patient.

15 Wishnofsky, M., and Byron, C. S. Carbohydrate Metabolism in Hypertension, *Arch. Int. Med.* **47** 790 (May) 1931.

16 Linder, G. C., Hiller, A., and Van Slyke, D. D. Carbohydrate Metabolism in Nephritis, *J. Clin. Investigation* **1** 247, 1925.

REPORT OF CASES

We shall present four cases (two of hyperthyroidism and two of hypertension) in which the respiratory quotient curve was the sole factor determining the nature of the disturbance in the metabolism of carbohydrates

The essential features of the first two cases (hyperthyroidism) are as follows

CASE 1—J A, a housewife, aged 49, had experienced tremors, palpitation, weakness, choking sensations, nervousness and profuse perspiration for the past two or three years. Her weight during this period was reduced from 175 to 170 pounds (79.4 to 77.1 Kg), a loss of 5 pounds (2.3 Kg)

There was a freely movable nodule as large as a walnut in the isthmus of the thyroid gland. The blood pressure was markedly labile (230 systolic and 110 diastolic on Sept 19, 1929, and 110 systolic and 80 diastolic on March 19, 1930). During the interval the systolic blood pressure was usually 170 or 190. The urine,

TABLE 2—*Curves for Blood Sugar and Respiratory Quotient in Two Cases of Hyperthyroidism*

	Case 1 (J A)		Case 2 (R B)	
	Blood Sugar	Respiratory Quotient	Blood Sugar	Respiratory Quotient
Fasting level	156*	0.763	115	0.75
45 minutes†	272		282	
75 minutes		0.850		0.75
120 minutes	272		277	
135 minutes		0.883		0.83

* Milligrams in 100 cubic centimeters of blood

† 1.75 Gm of dextrose per kilogram of body weight

examined on Aug 22, 1928, Sept 21, 1929, and March 21, 1930, was negative for sugar. The patient was on an unrestricted diet. The basal metabolic rate was plus 36 per cent on March 21, 1930.

CASE 2—R B, a housewife, aged 40, had experienced headache, dizziness, insomnia, palpitation and loss of weight (50 pounds [22.7 Kg]) during the past two years. She stated that glycosuria was discovered one year previously.

Physical examination showed diffuse enlargement of the thyroid gland, pulse rate, 124, blood pressure, 140 systolic and 70 diastolic, basal metabolism, plus 65 per cent. The blood sugar on May 6, 1929, was 0.166, and on Oct 4, 1929, 0.157 per cent.

A simultaneous study of the blood sugar curve and the respiratory curve was made. Each patient after fasting fourteen hours received 1.75 Gm of dextrose per kilogram of body weight. Three specimens of venous blood were taken from each patient—one at the "fasting level," and two at intervals of forty-five minutes and two hours after ingestion, respectively. The sugar content of the blood was determined by the Folin-Wu method. The respiratory quotient was determined at the "fasting level," and at intervals of one and one-quarter and two and one-quarter hours after ingestion, respectively. These intervals were chosen after careful consideration as best describing the nature of the curve. The gas was collected in a Tissot spirometer and analyzed by the method of Henderson and Haldane. The results are incorporated in table 2.

It will be noted that both cases showed "diabetic" blood sugar curves which were practically identical except that in case 2 the fasting level was only 115. Previous examinations, however, gave values above 150. Case 2 gave a history of glycosuria, whereas at no time was sugar found in the urine in case 1. It was postulated by one of us (M. W.¹⁷) that the blood sugar curve is the best index of the severity of diabetes mellitus. If both patients were diabetic the cases were of equal severity. The presence or absence of glycosuria is simply incidental to the renal threshold.

Since both patients suffered from hyperthyroidism, and as it has been abundantly shown that a high blood sugar curve occurs in a majority of such cases, it remained for the respiratory quotient curve to decide the nature of the disturbance in the metabolism of carbohydrates. It will be observed that in case 2 there was a low respiratory

TABLE 3—*Curves for Blood Sugar and Respiratory Quotient in Two Cases of Hyperthyroidism*

	Case 3 (T. S.)		Case 4 (J. W.)	
	Blood Sugar	Respiratory Quotient	Blood Sugar	Respiratory Quotient
Fasting level	133*	0.753	111	0.795
45 minutes†	205		214	
75 minutes		0.856		0.925
120 minutes	187		172	
135 minutes		0.848		0.963

* Milligrams in 100 cubic centimeters of blood

† 1.75 Gm. of dextrose per kilogram of body weight

quotient curve, whereas in case 1 the curve was normal. This study gave scientific proof that in case 2 the disturbance in the metabolism of carbohydrates was diabetic and that in case 1, nondiabetic.

A similar study was performed in two cases of hypertension. Practically all cases of hypertension show a high blood sugar curve, but the respiratory quotient curve is normal.¹⁵ They are therefore cases neither of potential nor of mild diabetes. Any case of mild diabetes among them can be determined only by a study of the respiratory quotient curve. This is well illustrated by table 3.

The patients in cases 3 and 4 were women, past 40, who had been suffering from hypertension (systolic blood pressure above 170 mm of mercury) for several years. At no time had dextrose been detected in the urine. It will be observed that both had high blood sugar curves. Whereas the respiratory quotient curve in case 4 was above normal,

¹⁷ Wishnofsky, M. The Use of the Dextrose Tolerance Test in the Determination of the Severity of Diabetes Mellitus, *Arch. Int. Med.* **42**: 443 (Sept) 1928.

that in case 3 was below normal. The disturbance in the metabolism of carbohydrate, shown in case 4, may therefore be considered to be nondiabetic, case 3, however, may be considered to be a potential or mild diabetes.

It is evident that the ultimate criterion in the determination of the presence of diabetes mellitus is the study of the respiratory quotient curve.

SUMMARY AND CONCLUSIONS

The disturbance in the metabolism of carbohydrates may be considered from three standpoints: the determination of the presence of glycosuria, changes in the concentration of sugar in the blood and changes in the respiratory quotient.

The renal threshold for dextrose varies from 45 to 348 mg per hundred cubic centimeters of blood. Glycosuria occurs in persons with a low renal threshold who are not diabetic. A diabetic person with a high threshold may have transient glycosuria or none.

A high level of sugar in the blood during fasting, and especially a high blood sugar curve after the ingestion of dextrose, may occur in conditions other than diabetes, such as hypertension, nephritis and hyperthyroidism.

From the scientific standpoint, the presence of glycosuria and hyperglycemia is inadequate for the diagnosis of diabetes mellitus.

A respiratory quotient curve that rises to 0.88 after the ingestion of an adequate amount of dextrose is indicative of a normal secretion of insulin, a low respiratory quotient curve, with certain exceptions, indicates a diminution in the secretion of insulin, or a neutralization or inactivation of an adequate supply.

In a study of both the blood sugar and the respiratory quotient curves after the ingestion of dextrose in two cases of hyperthyroidism and two of hypertension, it was demonstrated that the ultimate criterion in the diagnosis of diabetes mellitus is the respiratory quotient curve.

THE SIGNIFICANCE OF THE POTASSIUM-CALCIUM RATIO AND OF THE INORGANIC PHOSPHORUS AND CHOLESTEROL OF THE BLOOD SERUM IN ARTERIAL HYPERTENSION *

ALFRED A WEINSTEIN, A B

AND

SOMA WEISS, M D

BOSTON

The most significant abnormal feature of arterial hypertension, in the light of present knowledge, is the increased peripheral arteriolar resistance. Weiss and Ellis,¹ in 1930, attempted to measure the peripheral resistance quantitatively, and found that the average resistance of the arteriolar system of the greater circulation in a group of patients with hypertension was twice as great as in the normal control subjects. The factors, however, that are responsible for this increase in arteriolar resistance were not established.

The work of a number of investigators, such as Billigheimer,² Kraus and Zondek,³ Zondek,⁴ Kylin,⁵ and Spiro,⁶ indicated that the increased peripheral constriction of the vascular system is due to a disturbance of the vegetative nervous system. This altered function of the autonomic nervous system, according to these investigators, is accompanied by a change in the equilibrium of the blood through two powerful physiologic

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† From the Thorndike Memorial Laboratory, the Second and Fourth Medical Services (Harvard) of the Boston City Hospital, and the Department of Medicine of the Harvard University Medical School

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1 Weiss, S., and Ellis, L. B. The Quantitative Aspects and Dynamics of the Circulatory Mechanism in Arterial Hypertension, *Am Heart J* **5** 448, 1930

2 Billigheimer, E. Der Calciumspiegel im Blute und seine Beeinflussung durch verschiedene Gifte, *Klin Wchnschr* **1** 256, 1922

3 Kraus, F., and Zondek, S. G. Ueber die Durchtrankungsspannung, *Klin Wchnschr* **1** 1773, 1922

4 Zondek, S. G. Die Bedeutung des Antagonismus von Kalium und Calcium für die Physiologie und Pathologie, *Klin Wchnschr* **2** 382, 1923

5 Kylin, E. Der Gehalt des Blutes an Calcium und Kalium, *Acta med Scandinav*, 1927, supp 19, p 1

6 Spiro, P. Klinische Untersuchungen über das Calcium-Kalium-Gleichgewicht im Organismus, *Ztschr f klin Med* **110** 58, 1929

agents, potassium and calcium, with an increase in potassium, a decrease in calcium, and thus an increase in the potassium-calcium ratio. Other investigators, however, including Westphal,⁷ expressed the belief that changes in the osmotic relationships and permeability of the capillary bed and tissues, due to an increase in serum cholesterol, are responsible for elevated blood pressure.

EXPERIMENTAL AND CLINICAL OBSERVATIONS ON THE POTASSIUM-CALCIUM RATIO AND ITS RELATION TO THE AUTONOMIC NERVOUS SYSTEM AND THE ARTERIAL BLOOD PRESSURE

The theory that a change in the potassium content of the blood and the tissue fluids may influence the height of the blood pressure is supported by experimental observation. Mathison⁸ showed that potassium salts injected intra-arterially produce a rise in blood pressure. He also studied the effect of calcium in antagonizing the action of potassium on the blood pressure of spinal animals, and found that when equimolar quantities of potassium chloride and calcium chloride were injected intra-arterially, the blood pressure rose only slightly. He concluded that an increase in calcium tends to diminish the blood pressure, but that its action is not as pronounced as that of potassium in increasing the pressure. Harrison, Pilcher and Wilson⁹ observed no change in the cardiac output of dogs following the intravenous injection of potassium salts into the circulation. Chiari and Frolich¹⁰ claimed that the excitability of the sympathetic nervous system is markedly increased by diminishing the calcium content of the blood. Reid¹¹ suggested the hypothesis that a reduction of the calcium in the body removes or weakens the inhibitory influence of the vagus, and thus results in hypertension.

That there is an interdependence between stimulation of the autonomic nervous system and changes in the potassium-calcium equilibrium of the blood has been shown by several investigators. Kraus and Zondek¹² showed that stimulation of the vagus increased the potassium in

7 Westphal, K. Untersuchungen zur Frage der Entstehungsbedingungen des genuinen arteriellen Hochdruckes, *Ztschr f klin Med* **101** 559 and 584, 1925.

8 Mathison, G. C. The Effects of Potassium Salts upon the Circulation and Their Action on Plain Muscle, *J Physiol* **42** 471, 1911.

9 Harrison, T. R., Pilcher, C., and Wilson, C. P. The Effects of Calcium, Barium and Potassium on the Cardiac Output of Normal Dogs, *J Pharmacol & Exper Therap* **32** 55, 1928.

10 Chiari, R., and Frolich, A. Zur Frage der Nervenirregbarkeit bei der Oxalatvergiftung, *Arch f exper Path u Pharmacol* **66** 110, 1911.

11 Reid, W. D. Arterial Hypertension, Boston M & S J **192** 883, 1925.

12 Kraus, F., and Zondek, S. G. Zur Lehre vom Aktionsstrom, *Deutsche med Wchnschr* **47**:1513, 1921.

the tissues, giving rise to a local acidosis. The reverse holds true on stimulation of the sympathetic nerves. Wollheim¹³ and Benatt and Handel,¹⁴ working on hydrogen-hydroxyl equilibrium, contended that a preponderance of calcium increased the removal of the hydroxyl ion. Wollheim¹³ and Berg, Hess and Sherman¹⁵ observed that the cutting of the splanchnic nerve resulted in a fall in serum calcium, and that the cutting of the vagi resulted in a rise in calcium. Further recent work indicates not only that the sympathetic-parasympathetic balance determines the calcium-potassium ratio and thus the tissue reaction, but also that a change in this ratio may reverse the functional effect of nervous impulse on the innervated organ. Thus Kraus¹⁶ and Zondek¹⁷ demonstrated that if the calcium level is high, stimulation of the vagus augments rather than inhibits the action of the heart. Other investigators have shown that the action of the sympathetic nerves on the heart (Kohn and Pick¹⁸) and on the uterus (Turolt¹⁹) can be reversed. Finally, evidence is available (Konschegg,²⁰ Loewi,²¹ Zondek,²² Dressel and Jacobovitz,²³ Zondek and Reiter,²⁴ Barath,²⁵ Zondek and Ucko,²⁶

13 Wollheim, E. Vegetatives Nervensystem und Elektrolytverteilung, *Biochem Ztschr* **151** 416, 1924

14 Benatt, A., and Handel, M. Kalium- und Calcium Wirkung auf die Harnacidität, *Klin Wchnschr* **3** 1621, 1924

15 Berg, B. N., Hess, A. F., and Sherman, E. Changes in the Percentage of Calcium and Phosphorus of the Blood Following Section of the Sympathetic and Vagus Nerves, *J Exper Med* **47** 105, 1928

16 Kraus, F. Ueber die Wirkung des Kalziums auf den Kreislauf, *Deutsche med Wchnschr* **46** 201, 1920

17 Zondek, S. G. Ueber die Bedeutung der Calcium- und Kalium-Ionen bei Giftwirkungen am Herzen, *Arch f exper Path u Pharmakol* **87** 342, 1920

18 Kohn, R., and Pick, E. P. Ueber Aenderung der Adrenalinwirkung nach Erregung der vagalen Endapparate, *Arch f d ges Physiol* **184** 79, 1920

19 Turolt, M. Umkehr der Adrenalinwirkung auf den überlebenden Uterus, *Arch f Gynak* **115** 600, 1922

20 Konschegg, A. Ueber Beziehungen zwischen Herzmittel- und physiologischer Kationenwirkung, *Arch f exper Path u Pharmakol* **71** 251, 1913

21 Loewi, O. Ueber den Zusammenhang zwischen Digitalis- und Kalziumwirkung, *Arch f exper Path u Pharmakol* **82** 131, 1917

22 Zondek, S. G. *Arch f exper Path u Pharmakol* **88** 158, 1920, footnote 17

23 Dressel, K., and Jacobovitz, M. Untersuchungen über die theoretischen Grundlagen und die Indikationen der Calciumtherapie, *Klin Wchnschr* **1** 721, 1922

24 Zondek, H., and Reiter, T. Ueber das Wesen der Hormonwirkung, *Ztschr f klin Med* **99** 139, 1924

25 Barath, E. Kalziumwirkung und Blutzucker, *Med Klin* **2** 1372, 1924

26 Zondek, H., and Ucko, H. Die Zweiphasenwirkung der Hormone, *Klin Wchnschr* **4** 6, 1925

Kylin and Engel,²⁷ Zondek,²⁸ Kylin,²⁹ Zondek and Bernhardt,³⁰ Kylin³¹) that the effect of many drugs and hormones can be increased or reversed through changes in the local potassium-calcium equilibrium.

Since experimental observations suggest that changes in sympathetic-parasympathetic and potassium-calcium balance can be detected by their effect on the action of hormone, Kylin⁵ investigated the relation between the reaction to epinephrine and the potassium-calcium ratio. He observed that in practically all cases with a potassium-calcium ratio of from 1.7 to 2.15, which is within his normal range, there were normal reactions to epinephrine. The blood pressure curve of patients with essential hypertension having a quotient over 2.15 was consistently vagotonic, that is, the patients exhibited a drop in blood pressure after an injection of epinephrine. Dressel and Jacobovitz³² corroborated this work. In order to reestablish the potassium-calcium ratio and through it the normal sympathetic-parasympathetic balance, Kylin,³² in 1924, treated patients with essential hypertension with calcium-atropine and observed a drop in the blood pressure and a change in the reaction to epinephrine from vagotonic to sympathetotonic. Following these observations, series of analyses were made by different investigators on normal persons and patients with hypertension or other cardiovascular diseases, to determine the significance of these inorganic elements in the blood stream. Kylin,⁵ Brems³³ and Loewenstein³⁴ found a definite rise in potassium content from the normal level in cases of essential hypertension, while the calcium values were either at or below the

27 Kylin, E., and Engel, A. Ueber die Einwirkung der K-Ionen auf den Blutzuckerspiegel, *Klin Wchnschr* **4** 653, 1925.

28 Zondek, S. G. Die Identität von Nerv-Ionen und Giftwirkung, *Klin Wchnschr* **4** 809, 1925.

29 Kylin, E. Von der Bedeutung der K-Ionen für die Insulinwirkung, *Klin Wchnschr* **4** 1455, 1925.

30 Zondek, H., and Bernhardt, H. Ueber die Beeinflussbarkeit der Hypophysenhinterlappenextrakte, *Ztschr f klin Med* **101** 312, 1925.

31 Kylin, E. Ueber den Einfluss der Ca- und K-Ionen auf die Insulinwirkung, *Med Klin* **21** 1262, 1925, Ueber die Bedeutung der Elektrolyten für die Hormonwirkung, *ibid*, p. 1580, footnote 5.

32 Kylin, E. Ueber den Blutkalkspiegel bei der essentiellen Hypertonie, *Zentralbl f inn Med* **45** 471, 1924.

33 Brems, A. Ueber den Kalium- und Calcium-Gehalt des Blutserums unter normalen und unter gewissen pathologischen Verhältnissen, *Acta med Scandinav* **66** 473, 1927.

34 Loewenstein W. Chemische Blutbefunde bei der essentiellen Hypertension und ihre Bewertung, *Ztschr f klin Med* **107** 52, 1928.

normal lower limits In a series of cases, Kisch³⁵ observed a marked increase in potassium in patients with decompensated cardiac failure and an approximately normal amount in patients with compensated cardiac disease, regardless of the etiology and the level of the blood pressure Spiro,⁶ from a study of fifty-seven cases of vascular disorder, found that in patients with compensated circulation the potassium level was roughly within normal limits, both in the blood serum and in the corpuscles, although it tended toward the upper normal limits In patients with circulatory and renal failure, there was a distinct rise in the potassium of the corpuscles which paralleled the rise in serum potassium Since the flow of potassium from the corpuscles to the serum was less in persons with hypertension than in normal persons, Spiro concluded that the corpuscles acted as reservoirs, withdrawing and immobilizing the potassium as its level rose in the serum Moreover, he observed that the calcium level had a tendency to be low

Jansen³⁶ found a definite hypocalcemia in cardiac failure due to syphilis, nephrosclerosis and arterial hypertension In patients with arterial hypertension, with or without renal involvement but without cardiac failure, the calcium values were at the lower level of the normal range Anderson,³⁷ however, in sixteen cases of hypertension, observed normal calcium values as did Brems³³ in sixteen cases Brems, moreover, found no connection between the potassium-calcium ratio and the reaction to epinephrine Stieglitz³⁸ investigated forty-seven cases of pregnancy, with arterial hypertension as a secondary complication Forty cases, which included those of nonpregnant and pregnant women without hypertension, were observed as controls He found that the average calcium value in his pregnant patients coincided with that in his controls, and therefore he concluded that hypocalcemia is not a factor in the hypertension of pregnancy

Although the experimental and clinical observations do not reveal any undisputed relationships between the calcium content of the blood serum and arterial hypertension, nevertheless it is claimed that the ele-

35 Kisch, F Der Kalium- und Calcium-Gehalt des Gesamtblutes Kreislaufkranker und das Verhalten desselben unter dem Einfluss körperlicher Arbeit *Klin Wchnschr* **5** 1555, 1926

36 Jansen, W H Der Kalkgehalt des menschlichen Blutes unter pathologischen Verhältnissen, *Deutsches Arch f klin Med* **144** 14, 1924

37 Anderson, W T Meddelende fra Tursens medisinske Lyseminstitut, *Hospitalstid* **68** 1177, 1925

38 Stieglitz, E J Hypertension in Pregnancy, *Arch Int Med* **39** 465 (April) 1927

vation of blood calcium results in a fall of the blood pressure in arterial hypertension Addison³⁹ claimed that the daily ingestion of from 4 to 12 Gm of calcium chloride for four weeks resulted in a drop in the blood pressure In 1930, Secher⁴⁰ stated that the intramuscular injection of parathyroid extract caused a simultaneous rise in the blood calcium and a drop in the blood pressure He claimed that hypertension is due to an insufficient functioning of the parathyroid gland, and asserted that specimens of parathyroid obtained at autopsy from patients who had had hypertension show characteristic atrophy of the hormone-producing cells

EXPERIMENTAL AND CLINICAL OBSERVATIONS ON THE CHOLESTEROL LEVEL AND ITS RELATION TO ARTERIAL BLOOD PRESSURE

Westphal,⁷ on feeding rabbits on a high cholesterol diet, observed that their blood pressure rose with an increase in the serum cholesterol This increase in the blood pressure, he maintained, was independent of a disturbance of vasomotor function or internal secretion, and was due to the sensitizing effect of cholesterol on the muscle walls of the vessels He expressed the belief that the sensitized muscular elements of the vessels then responded with increased contraction to substances in the blood serum The experimental observations of Westphal have been supported also by the observations of Schmidtman⁴¹ and Fahr⁴² Schonheimer⁴³ and Shapiro,⁴⁴ however, found no relationship between the cholesterol level of the blood and high blood pressure Furthermore, experiments involving injection of cholesterol into the blood stream have given contradictory results Thomas,⁴⁵ in 1926, observed a rise in the blood pressure in four rabbits after injections of cholesterol

39 Addison, W L T The Use of Calcium Chloride in Arterial Hypertension, *Canad M A J* **14** 1059, 1924

40 Secher, K Eine Untersuchung uber die Ursachen der Hypertomie, *Acta med Scandinav* **73** 309, 1930

41 Schmidtman, M Experimentelle Studien zur Pathogenese der Arteriosklerose, *Virchows Arch f path Anat* **237** 1, 1922

42 Fahr, T Beitrage zur experimentellen Atherosklerose unter besonderer Berucksichtigung der Frage nach dem Zusammenhang zwischen Nebennierenveranderungen und Atherosclerose, *Verhandl d deutsch path Gesellsch* **12** 125, 1922

43 Schonheimer, R Ueber die experimentelle Cholesterinkrankheit der Kaninchen, *Virchows Arch f path Anat* **249** 1, 1924

44 Shapiro, S Studies in Atherosclerosis The Relation of Glands of Internal Secretion to Its Development, *M J & Rec* **126** 284, 1927

45 Thomas, E Recherches expérimentales touchant l'influence de la cholestérine sur le developpement de l'hypertension artérielle, *Arch d mal du coeur* **19** 641, 1926

Tholldte ⁴⁶ was unable to verify the experimental observations of Westphal ⁷ and Schmidtman ⁴¹

Westphall,⁷ investigating a series of eighty cases of essential hypertension, found that the cholesterol level was above the normal range in 71 per cent of the cases. Weil and Guillaumin⁴⁷ found high cholesterol values in the plasma of patients with hypertension. Askanazy⁴⁸ observed a hypercholesteremia in most of his cases of hypertension. Thus, on the basis of observations on man and experiments on animals, Westphal and others considered that cholesterol is one factor in the genesis of essential hypertension.

However, Mjassnikow⁴⁹ claimed that hypercholesteremia was present in less than 50 per cent of his cases in which atherosclerosis was only weakly developed. Loewenstein³⁴ reported only one case of hypercholesteremia among fifty cases of hypertension investigated. Harris and Lipkin⁵⁰ also found normal cholesterol values in ten of eleven patients with hypertension. Moreover, intramuscular injections of cholesterol that raised the cholesterol level of the serum markedly in four cases of hypertension were unassociated with any changes in blood pressure.

THE PROBLEM

With the elimination of the two supposed constrictor substances in the circulating blood, guanidine and amino-acids, as etiologic agents in the development of the increased peripheral resistance in arterial hypertension, the claims of the proponents of the potassium, calcium and cholesterol hypotheses have gained significance. A definite confirmation of these hypotheses by direct observations would also offer a rational therapeutic approach to arterial hypertension. Since the observations quoted by previous investigators in this field are open to dispute, both because of the faulty and inaccurate methods used and because of insufficient information concerning the clinical condition of the patients, this investigation was undertaken to determine whether or not changes can be demonstrated in the level of the potassium, calcium

46 Tholldte, M. Hypercholesterinämie, Blutdruck und Gefässveränderungen im Tierversuch, Beitr z path Anat u z allg Path **77** 61, 1927.

47 Weil, M. P., and Guillaumin, C. O. Hyperglycémie, hypercholesterinémie augmentation des composés uriques globulaires et hypertension artérielle variable, son origine rénale, Ann de med **19** 415, 1926.

48 Askanazy. Hypertonie und Hypercholesterinämie, München med Wchnschr **74** 1793, 1927.

49 Mjassnikow, G. L. Klinische Beobachtungen über Cholesterinämie bei Arteriosklerose, Ztschr f klin Med **102** 65, 1926.

50 Harris, I., and Lipkin, I. J. High Blood Pressure and Cholesterol, Brit M J **1** 587, 1930.

and cholesterol of the blood when tested by the reliable methods available and when the patients are selected after a detailed investigation of the clinical state. Moreover, since the calcium level of the blood varies inversely with the inorganic phosphate level, all other things being equal (Binger,⁵¹ Salvesen and Linder,⁵² Peters and Eiserson⁵³), an increase in the average inorganic phosphate level would corroborate any evidence of a decrease in the average calcium level. Hence, the better to control the observations on calcium indirectly, determinations of the inorganic phosphate level were also performed. Finally, if changes actually take place in the potassium-calcium ratio in arterial hypertension, it would be significant to ascertain whether such a change is associated with an alteration in the cholesterol level.

METHODS

The chemical methods used have been devised recently and, with the exception of the cholesterol method, gave satisfactory results throughout the course of the investigations.

Potassium was determined by the method developed by Taylor.⁵⁴ Duplicate analyses by this method gave results which agreed within 2 per cent. One minor change was adopted in this procedure. It was found that a gel of anhydrous tungstic acid formed when the standard solutions were evaporated to dryness. To obviate this difficulty, the standard solutions were evaporated only to 2 cc. Satisfactory precipitation of potassium was then obtained by the addition of 2 cc. of sodium cobaltinitrite and 2 cc. of 95 per cent alcohol.

The method for the determination of calcium that was developed by Fiske and Logan⁵⁵ offered no difficulties. At the suggestion of Taylor,⁵⁶ the following changes were made in this procedure for convenience and speed. 1. The precipitation of the calcium was completed in one and one-half hours instead of in twelve. Results obtained by using this modification checked within 1 per cent of those obtained

51 Binger, C. Toxicity of Phosphates in Relation to Blood Calcium and Tetany, *J. Pharmacol. & Exper. Therap.* **10** 105, 1917.

52 Salvesen, H. A., and Linder, G. C. Observations on the Inorganic Bases and Phosphates in Relation to the Protein of Blood and Other Body Fluids in Bright's Disease and in Heart Failure, *J. Biol. Chem.* **58** 617, 1923.

53 Peters, J. P., and Eiserson, L. The Influence of Protein and Inorganic Phosphorus on Serum Calcium, *J. Biol. Chem.* **84** 155, 1929.

54 Taylor, F. H. L. The Determination of Potassium in Blood Serum, *J. Biol. Chem.* **87**:27, 1930.

55 Fiske, C. H., and Logan, M. A. To be published, *J. Biol. Chem.*

56 Taylor, F. H. L. Personal communications to the authors.

from precipitations obtained over a period of twelve hours 2 The fifteen-thousandths normal hydrochloric acid was replaced by hundredth normal acid Two cubic centimeters of the hundredth normal acid was added to the ignited calcium oxide instead of 1 cc of the fifteen-thousandths normal acid, and titrated by hundredth normal sodium hydroxide

The method of Fiske and Subbarow⁵⁷ was used for the determination of inorganic phosphorus, and it was quite satisfactory The method for the saponification of cholesterol of Bloor, Pelkan and Allen⁵⁸ was accurate within only from 7 to 10 per cent

RESULTS

Seventy-five cases of hypertension, twenty-four in males and fifty-one in females, between the ages of 19 and 75 years, were studied Twenty-nine of these cases exhibited clinical evidence of cardiac failure, six showed clinical evidence of renal involvement and three exhibited both cardiac and renal involvement so far as could be ascertained by clinical and laboratory studies Of the seventy-five cases, forty-five showed clinical evidence of arteriosclerosis All patients were in the hospital for at least one week previous to the tests Blood samples were obtained in the postabsorptive state at 8 a m from the cubital vein and were analyzed immediately Measurements of the blood pressure were obtained with the patient in the horizontal position The systolic pressure ranged between 155 and 270 mm of mercury, the diastolic between 70 and 160 mm, the average systolic pressure was 189 mm, the average diastolic, 105 mm

Table 1 presents the potassium, calcium, cholesterol and inorganic phosphorus content of the blood serum as well as the potassium-calcium and calcium-phosphorus ratios in seventy-five cases of hypertension with and without secondary complications Table 2 presents the results of similar measurements in twenty-five control cases without hypertension The values presented in table 2 compare favorably with those reported recently by other authors using the same methods

The calcium in the Fiske-Logan method was about 0.6 mg per hundred cubic centimeters of serum less than that reported by authors using the Kramer-Tisdall or Jansen methods, for three reasons 1 The former methods involved the oxidation of the calcium

57 Fiske, C. H., and Subbarow, Y. Colorimetric Determination of Phosphorus, *J Biol Chem* **66** 375, 1925

58 Bloor, W. R., Pelkan, K. F., and Allen, D. M. Determination of Fatty Acids (and Cholesterol) in Small Amounts of Blood Plasma, *J Biol Chem* **52** 191, 1922

TABLE 1—*The Potassium, Calcium, Cholesterol and Inorganic Phosphorus Content and the Potassium-Calcium and Calcium-Phosphorus Ratios of the Blood Serum in Seventy-Five Cases of Arterial Hypertension*

Case	Age	Sex	Arterial Blood Pressure		Pulse Pressure, Mm Mercury	Cardiac (C) or Renal (R) Impairment	Potassium, Mg	Calcium, Mg	Cholesterol, Mg	Phosphorus, Mg	Potassium Calcium Ratio	Calcium Phosphorus Ratio
			Systolic, Mm Mercury	Diastolic, Mm Mercury								
1	67	M	160	80	80	C	29.20	8.80	165.5	3.62	3.32	2.43
2		F	170	75	95		23.98	8.77	164.5	3.85	2.73	2.28
3	55	F	180	90	90	C	23.15	9.77	153.4	3.81	2.37	2.56
4	66	F	195	120	75	C	24.00	9.60	160.1	4.30	2.50	2.23
5	69	F	195	115	80		20.00	11.50	166.6	4.60	1.74	2.50
6	75	F	175	105	70	C	23.51	9.92	174.6	4.73	2.37	2.10
7	75	F	210	100	100		20.40	9.97	122.4	3.42	2.05	2.92
8	60	F	155	110	45		24.84	9.58	297.4	4.97	2.59	1.93
9		F	216	120	96		21.20	10.26	271.8	4.13	2.05	2.48
10	40	M	180	100	80	C	25.31	9.20	167.7	4.30	2.75	2.14
11		M	185	140	55	C	22.47	9.80	223.2	4.73	2.29	2.07
12		M	180	110	70	C	20.00	9.99	268.8	3.86	2.02	2.59
13	19	M	165	75	90	C	24.70	9.10	182.9	5.10	2.71	1.78
14	62	F	235	125	110		20.30	9.92	196.8	4.06	2.00	1.94
15	62	F	220	120	100	R	21.73	9.40	260.3	4.21	2.31	2.23
16	64	F	242	120	122	C R	26.20	9.38	206.5	4.32	2.79	2.17
17	72	F	170	130	40	C	21.51	10.72	227.2	4.00	2.01	2.68
18	40	M	170	95	75		22.33	9.61	201.0	4.20	2.35	2.09
19	72	F	205	100	95	C R	25.00	10.06	240.2	4.20	2.49	1.90
20	72	F	190	100	90	C	23.52	10.20	156.3	3.20	2.31	3.18
21	61	F	180	95	85	R	20.00	9.67	247.4	3.60	2.07	2.69
22	19	F	160	80	80		20.15	9.60	134.6	3.00	2.10	3.20
23	69	F	210	100	110	C	19.60	8.00	208.3	3.36	2.45	3.00
24	64	F	185	100	85	C	22.86	11.60	223.2	2.95	1.97	3.93
25	60	F	186	110	76	C	21.39	9.54	196.8	4.00	2.29	2.38
26		F	198	100	98	C	21.05	9.05	181.1	3.26	2.33	2.78
27	60	F	180	90	90	C	22.22	9.60	211.9	5.59	2.32	1.72
28	68	F	230	120	110	C	18.69	9.60	183.8	3.85	1.95	2.49
29	67	M	200	100	100		18.27	9.70	219.3	3.13	1.88	3.10
30	45	F	170	90	80		23.53	10.30	250.0	4.70	2.29	2.19
31	42	F	170	110	60	R	24.24	9.60	223.2	6.06	2.51	1.58
32	68	M	170	70	100	C R	23.39	10.24	210.1	2.68	2.28	3.82
33	50	M	175	120	55	R	21.62	10.80	192.5	3.98	2.00	2.71
34	47	M	195	120	75	C R	17.86	10.12	238.0	3.94	1.77	2.57
35	30	F	230	144	86	R	22.86	9.50	231.5	6.84	2.41	1.89
36	73	F	170	90	80		20.83	10.70	347.2	4.30	1.95	2.49
37	74	F	190	125	65	C	20.00	9.20	187.9	2.33	2.17	2.71
38		F	180	110	70		20.10	9.20	221.2	3.56	2.14	2.64
39	60	F	160	80	80		21.62	9.40	168.9	3.92	2.30	2.39
40	60	F	175	78	97		20.83	10.69	147.9	4.68	1.95	2.29
41	68	F	176	112	64	C	20.83	10.17	177.3	4.02	2.05	2.53
42	66	F	162	74	88		21.74	10.19	233.6	4.10	2.14	2.48
43	52	F	225	125	100		18.71	10.19	191.7	4.00	1.84	2.55
44	51	F	160	100	60		19.40	10.77	238.0	3.33	1.76	3.25
45	75	M	170	100	70		19.31	9.36	170.1	3.32	2.06	2.74
46	58	M	180	110	70		25.01	9.56	225.2	3.81	2.59	2.54
47	77	M	160	95	65	C	21.02	9.67	169.6	2.94	2.18	3.29
48	73	M	160	100	60	C	22.34	8.97	195.3	2.74	2.49	3.27
49	73	F	220	90	130		22.27	9.17	174.8	3.38	2.53	2.71
50	65	F	170	86	84		24.56	11.23	251.8	4.38	2.10	2.57
51	50	F	255	134	120	C	24.09	10.08	155.3	4.44	2.39	2.27
52	21	F	145	80	65		19.31	10.08	168.3	4.09	1.92	2.46
53	62	F	208	124	84		20.42	10.28	201.6	4.44	1.99	2.31
54	38	M	148	110	38	R	19.23	8.65	208.5	3.57	2.28	2.42
55	56	M	184	120	64	C	20.60	8.78	156.1	3.83	2.35	2.29
56	44	M	220	150	70		22.99	9.23	208.3	4.47	2.49	2.06
57	47	M	190	110	80		17.39	9.43	245.1	4.37	1.84	2.16
58	40	F	160	90	70		19.14	9.43	219.5	4.76	2.03	1.98
59	47	F	170	120	50		22.86	9.21	192.3	5.63	2.48	1.64
60	59	F	215	130	85		22.73	9.97	185.2	4.21	2.28	2.37
61	60	F	165	98	67	C	24.24	9.97	192.3	4.68	2.49	2.13
62	52	F	200	110	90		21.98	9.43	200.0	3.90	2.33	2.42
63	43	F	150	70	80	C	26.63	9.11	138.8	4.21	2.92	2.16
64	65	F	210	86	124	C	21.74	9.65	183.5	3.85	2.25	2.18
65	53	M	260	160	100	C	23.12	9.61	225.2	3.90	2.41	2.46
66	46	F	230	140	90		22.86	9.78	294.2	4.20	2.33	2.33
67	64	M	190	90	100		23.33	9.83	171.2	3.72	2.37	2.64
68	32	M	145	90	55	C	23.33	10.53	208.3	4.13	2.24	2.55
69	58	M	190	70	120		21.85	9.32	174.2	4.63	2.35	2.01
70	74	F	270	130	140		23.26	9.76	226.2	4.94	2.38	1.98
71	56	F	205	105	100		23.95	9.16	227.3	3.49	2.63	2.61
72	47	M	212	118	94		22.99	10.43	148.8	4.65	2.20	2.24
73	60	M	200	95	105		22.60	9.55	166.7	4.38	2.37	2.18
74	60	F	220	110	110	C	26.66	9.17	271.7	4.00	2.91	2.29
75	69	F	195	75	120		24.24	9.95	255.1	5.26	2.44	1.89
Average							22.15	9.75	204.5	4.09	2.28	2.43

oxalate precipitate by dilute potassium permanganate. Any organic material brought down by the precipitate would obviously increase the final calcium value. 2 Unless the p_H of the solution is carefully con-

TABLE 2—*The Potassium, Calcium, Cholesterol and Inorganic Phosphorus Content and the Potassium-Calcium and Calcium-Phosphorus Ratios of the Blood Serum in Twenty-Five Control Cases*

Case	Age	Sex	Arterial Blood Pressure			Diagnosis and Comments	Potassium, Mg	Calcium, Mg	Cholesterol, Mg	Phosphorus, Mg	Potassium Calcium Ratio	Calcium Phosphorus Ratio
			Systolic, Mm Mercury	Diastolic, Mm Mercury	Pulse Pressure, Mm Mercury							
1	50	F	126	85	41	Cinchona bark poisoning	19.80	10.62	192.3	4.42	1.86	2.40
2	65	F	120	60	60	Gastro enteritis	18.18	9.40	161.3	3.05	1.93	3.01
3	65	M	110	50	60	Lymphoblastoma	20.40	9.90	161.3	3.68	2.06	2.72
4	65	F	130	84	46	Cancer of stomach?	17.17	10.90	126.2	4.68	1.58	2.33
5	46	F	142	84	56	Frontal sinusitis	20.20	10.50	162.3	4.04	1.93	2.60
6	52	F	135	85	50	Myxedema, secondary anemia	19.01	9.80	131.6	4.94	2.02	1.98
7	60	M	138	70	68	Gout, infectious arthritis, arterio sclerosis	20.20	9.37	120.6	4.06	2.16	2.31
8	75	M	145	80	65	Chronic constipation	18.50	9.51	206.5	3.42	1.96	2.78
9	49	M	135	70	65	Diabetes mellitus, tabes dorsalis	19.90	9.60		3.39	2.07	2.83
10	62	M	125	75	50	Lobar pneumonia, mild arterio sclerosis	20.00	9.32	151.2	4.09	2.15	2.28
11	68	F	125	80	45	Ulcer or cancer of stomach, arterio sclerosis	20.83	9.65	250.0	4.76	2.16	2.03
12	49	M	135	90	45	Bronchopneumonia	18.90	10.00	165.5	3.04	1.89	3.29
13	60	F	135	85	50	Cancer of stomach	21.05	9.43	189.2	5.23	2.23	1.80
14	65	M	130	65	65	Pleurisy, arterio sclerosis	21.97	9.44	208.3	4.71	2.33	2.00
15	69	F	125	60	65	Lobar pneumonia, generalized arterio sclerosis	21.51	9.40	271.7	4.97	2.29	1.89
16	55	F	110	60	50	Diabetes, arterio sclerosis	20.20	10.69	195.3	4.23	1.89	2.33
17	40	M	130	95	35	Tumor of the brain or subarachnoid hemorrhage	21.00	9.80	137.3	4.14	2.14	2.48
18	55	F	125	58	67	Bronchopneumonia	18.60	10.03	142.9	3.76	1.86	2.67
19	78	F	125	50	75	Cancer of cecum	18.18	8.80	133.0	4.71	2.07	1.87
20	60	M	135	80	55	secondary anemia	21.62	9.30	204.9	4.82	2.32	1.93
21	42	M	125	80	45	Arteriosclerosis tertiary syphilis	18.02	9.65	195.3	4.79	1.87	2.01
22	40	M	130	80	50	Alcoholic neuritis, "Jamaica ginger" paralysis	21.50	9.54	164.2	4.01	2.25	2.38
23	59	M	135	85	50	Neuritis and obesity	21.27	10.12	260.3	4.97	2.10	2.04
24	42	F	130	90	40	Pleurisy	23.53	9.73	195.3	5.40	2.42	1.80
25	54	F	140	90	50	Pleurisy	18.18	10.23	162.3	4.30	1.78	2.38
						Peptic ulcer	18.18	10.23	162.3	4.30	1.78	2.38
Average							19.99	9.79	171.6	4.30	2.05	2.33

trolled, magnesium oxalate is also precipitated. 3 Since the calcium is precipitated by the oxalate ion, the incomplete removal of the precipitating medium would again raise the calcium value. These sources of error are eliminated in the Fiske-Logan method by the precipitation of the normal blood serum which has a p_H of about 7.4, and by igniting

the calcium oxalate precipitate to remove organic material and the excess oxalate ion

Table 3 contains a comparison of the range and average values of potassium, calcium, cholesterol and inorganic phosphorus in the serum in cases in which there was hypertension and in cases in which hypertension was not present. The cases with hypertension have been subdivided into three groups: (1) cases of uncomplicated hypertension,

TABLE 3—*The Average and Maximal Variations of the Potassium, Calcium, Cholesterol and Inorganic Phosphorus Content and the Potassium-Calcium Ratio and Calcium-Phosphorus Ratio of the Blood Serum in Seventy-Five Cases with Hypertension and in Twenty-Five Control Cases **

	Num ber of Cases	Potassium		Calcium		Cholesterol	
		Range	Aver age	Range	Aver age	Range	Aver age
Control	25	17.2-23.5	20.00	8.8-10.9	9.80	120.6-260.3	171.6
Essential hypertension	37	17.4-25.0	21.68	9.2-11.5	9.88	134.0-297.4	212.7
Hypertension with renal impairment	9	17.9-26.2	22.10	8.6-10.8	9.68	192.5-260.3	227.0
Hypertension with cardiac impairment	32	18.7-29.2	22.80	8.0-10.7	9.62	138.8-271.7	194.0
Hypertension with and without complications	75	17.4-29.2	22.15	8.0-11.5	9.75	134.0-297.4	204.5

	Num ber of Cases	Phosphorus		Potassium Cal cium Ratio		Calcium Phos phorus Ratio	
		Range	Aver age	Range	Aver age	Range	Aver age
Control	25	3.0-5.4	4.3	1.78-2.42	2.05	1.8-3.0	2.33
Essential hypertension	37	3.0-5.6	4.1	1.74-2.63	2.19	1.6-3.2	2.41
Hypertension with renal impairment	9	3.6-6.8	4.5	1.77-2.79	2.29	1.6-2.7	2.18
Hypertension with cardiac impairment	32	2.3-5.6	3.9	1.77-3.32	2.38	1.7-3.9	2.50
Hypertension with and without complications	75	2.3-6.8	4.1	1.74-3.32	2.32	1.6-3.9	2.43

* All values are expressed in milligrams per hundred cubic centimeters of blood serum

(2) cases of hypertension with renal involvement, (3) cases of hypertension with cardiac failure. Table 3 shows that the average potassium level tends to increase from a level of 20 mg per hundred cubic centimeters of serum in control cases, to 22.15 mg per hundred cubic centimeters in cases of hypertension with and without involvements. When the cases were separated clinically into groups according to complications, those with cardiac involvement showed an average level of 22.8 mg, those with renal involvement, 22.1 mg, and the uncomplicated cases of hypertension, 21.68 mg per hundred cubic centimeters of serum.

When the potassium level was charted against the systolic pressure (chart 1) the potassium value rose distinctly from 20 to 22 mg per hundred cubic centimeters of serum, between the systolic range of from 150 to 180 mm of mercury. From that point the rise seemed to be approaching a limit, for at a systolic pressure of 230, the potassium level

was only 22.5 mg per hundred cubic centimeters of serum. A similar relation was found when the potassium values were charted against the diastolic pressure. This elevation of the potassium level with the blood pressure is largely due to the relatively high potassium values in patients with circulatory failure, as will be shown presently.

As indicated in chart 2, no change was observed in the calcium level. The average calcium level in twenty-five control cases was found to be 9.8 as compared with 9.75 mg per hundred cubic centimeters of serum in seventy-five cases of hypertension with or without complications. The latter group, when subdivided, showed a calcium level of

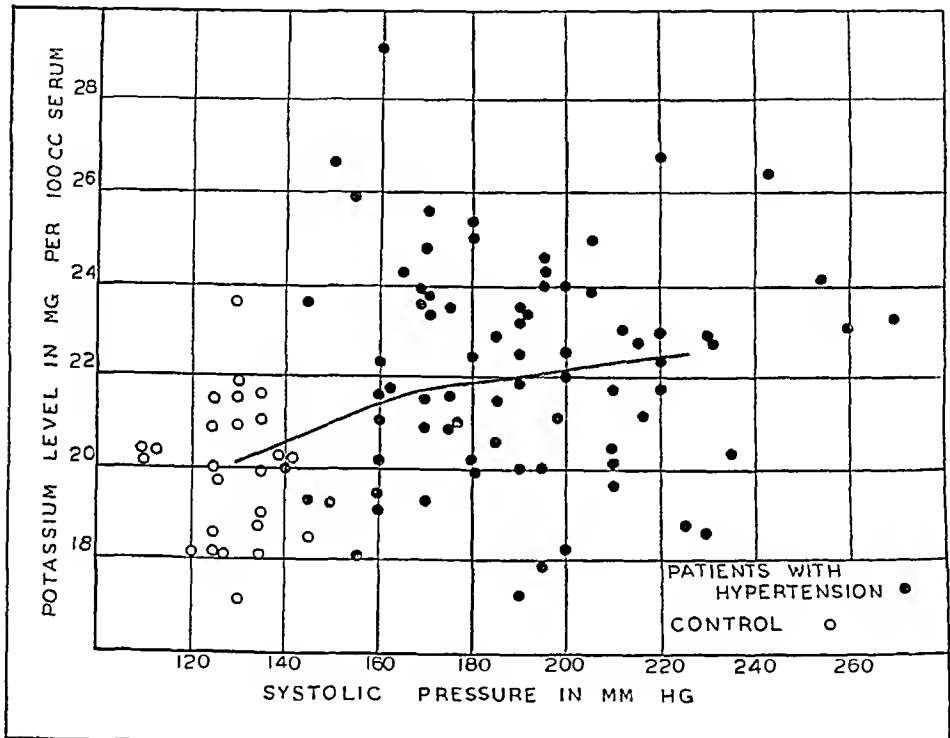


Chart 1—The distribution of the potassium level in the blood serum and its relation to the height of the systolic blood pressure in seventy-five patients with hypertension and in twenty-five control cases

9.88 mg per hundred cubic centimeters of serum for uncomplicated cases of hypertension, 9.68 mg for cases with renal involvement, and 9.62 mg for cases with cardiac decompensation. Since the calcium method was accurate only within 1 per cent, the average calcium level of these groups was well within the limits of the observations on the controls. The observed range of calcium values for the control cases was from 8.8 to 10.9 mg per hundred cubic centimeters of serum, or very similar to the range in the cases of uninvolved hypertension (9.2 to 11.5 mg per hundred cubic centimeters). Moreover, when the calcium level of the hundred cases studied was plotted against the systolic or

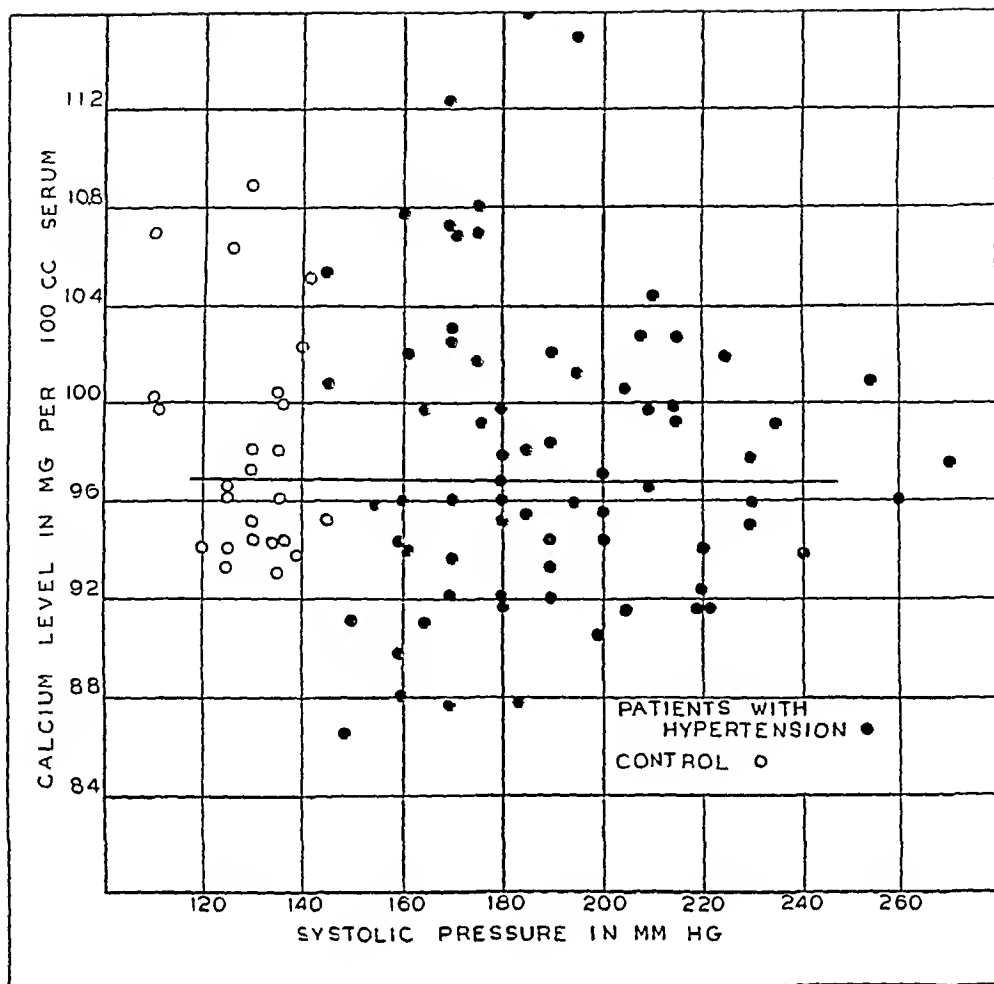


Chart 2—The distribution of the calcium level in the blood serum and its relation to the height of the systolic blood pressure in seventy-five patients with hypertension and in twenty-five control cases

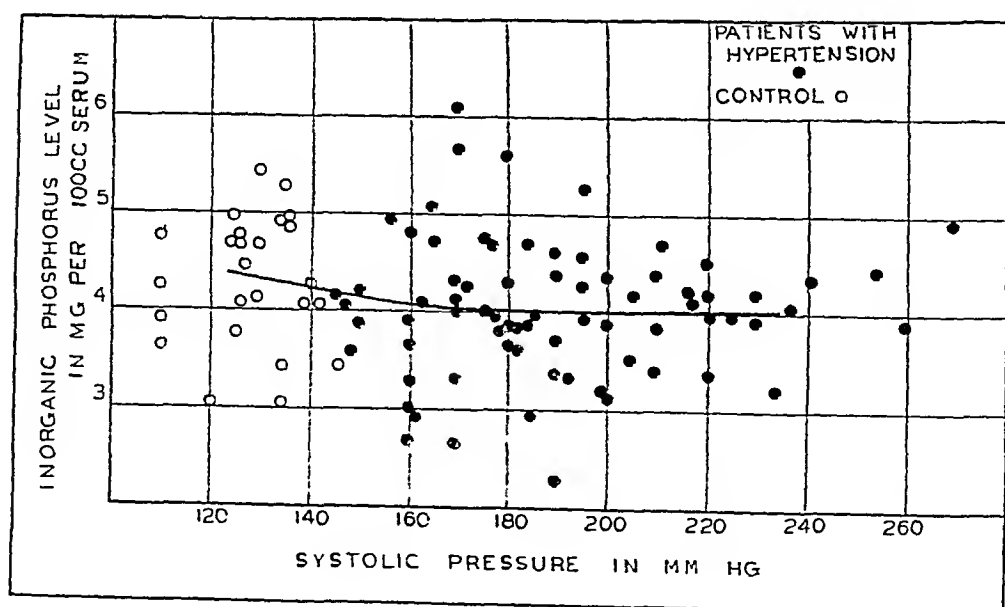


Chart 3—The distribution of the inorganic phosphorus level in the blood serum and its relation to the height of the systolic blood pressure in seventy-five patients with hypertension and in twenty-five control cases

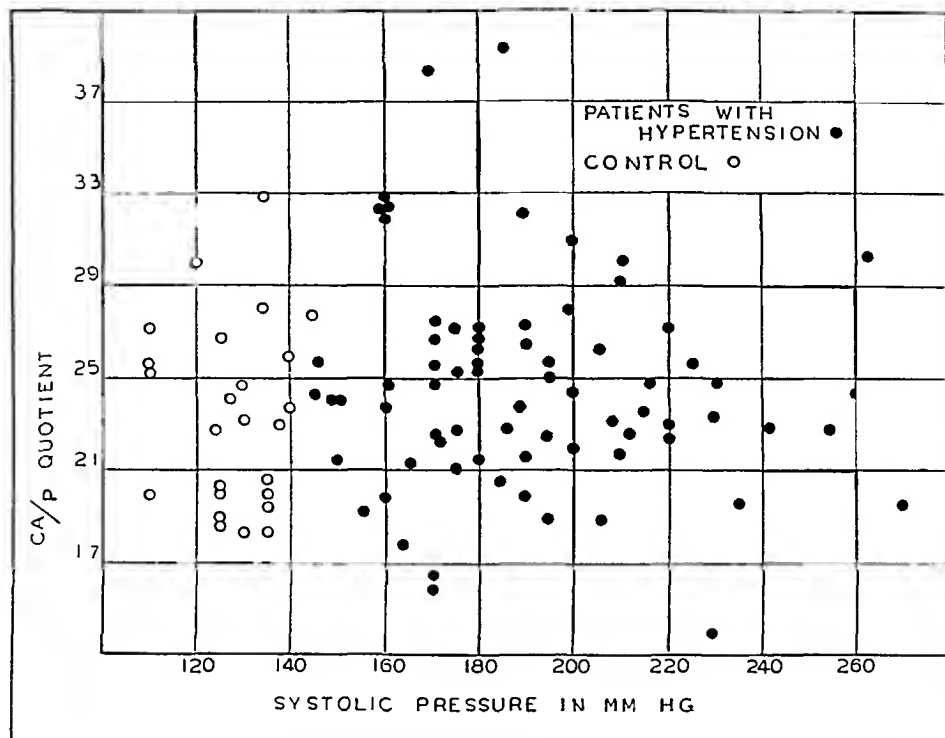


Chart 4—The distribution of the values for the calcium-inorganic phosphorus ratio in the blood serum and its relation to the height of the systolic blood pressure in seventy-five patients with hypertension and in twenty-five control cases

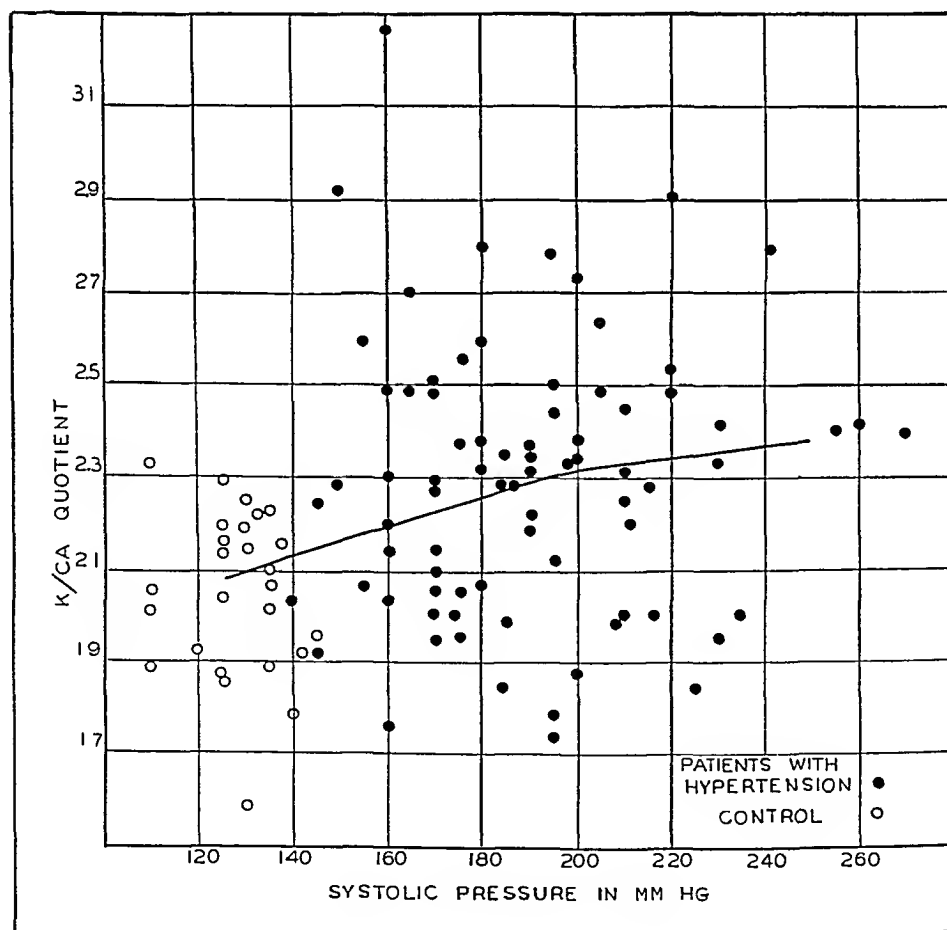


Chart 5—The distribution of the values for the potassium-calcium ratio in the blood serum and its relation to the height of the systolic blood pressure in seventy-five patients with hypertension and in twenty-five control cases

diastolic blood pressure, the calcium level showed no tendency to rise as the blood pressure rose

The observations on the inorganic phosphorus level corresponded to those on the calcium level, for the inorganic phosphorus level in seventy-five cases of mixed hypertension (4.1 mg per hundred cubic centimeters), showed no tendency to increase, as one would expect if the calcium level were to decrease (chart 3) Also the calcium-inor-

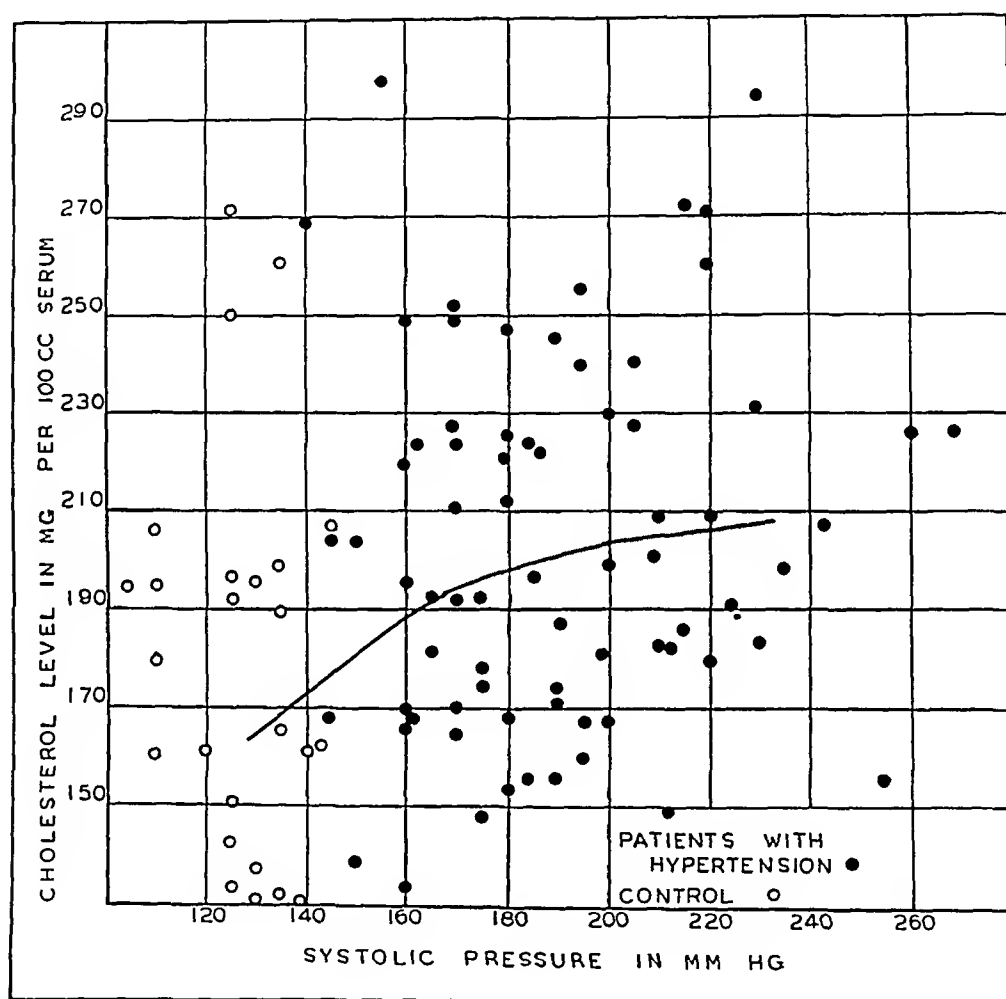


Chart 6—The distribution of the cholesterol level in the blood serum and its relation to the height of the systolic blood pressure in seventy-five patients with hypertension and in twenty-five control cases

ganic phosphorus ratios in the seventy-five cases of hypertension (2.4), showed no tendency to decrease. In hypertension with renal involvement, however, since renal dysfunction permits a greater retention of inorganic phosphorus, this ratio dropped to 2.18 (chart 4).

The values for the potassium-calcium ratio roughly followed the potassium values, for the quotient rose from 2.05 for the control group, to 2.32 for the entire group of patients with hypertension. Divided into groups, the ratio of the uninvolved group was 2.19, that of the group

with cardiac involvement was 2.38, and that of the group with renal involvement was 2.29. Plotted against the systolic or diastolic pressure, the potassium-calcium quotient showed the same type of curve as potassium. It rose from 2.1 at 140 mm to 2.32 at 200 mm of mercury (chart 5). The explanation of this will be discussed later.

The blood cholesterol also showed a rise in level from a control average of 171.6 to 204.5 mg per hundred cubic centimeters of blood in cases of mixed hypertension. In nine cases of hypertension with renal involvement, the level rose to 227 mg, corresponding to previous observations on increase in blood cholesterol with renal dysfunctions.

Plotted against the systolic or diastolic pressure, the cholesterol rose from 170 mg per hundred cubic centimeter of blood at 140 mm to 200 mg per hundred cubic centimeter of serum at 200 mm of mercury (chart 6).

COMMENT

The observations indicate that the seventy-five cases of hypertension with or without secondary complication showed an average increase of 9 per cent in the potassium of the blood serum above the average level of the control group. Division of the cases of hypertension into groups shows that the cases without renal or cardiac involvement showed an average increase of 7.7 per cent as compared with an increase of 5.2 per cent in cases with renal involvement, and an increase of 12.2 per cent in cases of cardiac decompensation. The following are the most plausible interpretations for these differences: 1. Changes that take place in cardiovascular dysfunction affect the potassium metabolism of the body in such a way as to cause an increase in blood potassium. 2. Changes that take place in the parasympathetic-sympathetic balance so affect the potassium-calcium ratio that the blood pressure rises, and renal and cardiac failure develop as secondary involvements. 3. An overactivity of the parasympathetic nervous system occurs in a few instances, and this produces an increase in the blood potassium which in turn affects the arteriolar system or the blood pressure. The first of the foregoing inferences is probably correct, for in thirty-seven cases of uninvolved hypertension, normal potassium values were present in 78 per cent and high values in only 21 per cent, likewise, 65 per cent showed normal potassium-calcium values, and only 29 per cent, high values. If changes in this ratio are factors in the etiology of hypertension, it is difficult to explain why only eleven of the thirty-seven uncomplicated cases of hypertension (29 per cent) showed high quotients. If, however, these changes in potassium level and potassium-calcium quotient are indicative of altera-

tions in cardiorenal function, then it becomes plausible that 56 per cent of the cases of hypertension with renal involvement and 63 per cent of those with cardiac involvement showed abnormally high potassium-calcium quotients. Moreover, since the potassium-calcium ratio for the thirty-seven uncomplicated cases of hypertension was 2.19 (as compared with a value of 2.05 in the control cases) which is well within the normal range of from 1.78 to 2.35, and since this ratio was only correct within 6 parts in 200, it would be hazardous to say that this slight rise in the ratio led to hypertension or was indicative of a change in parasympathetic-sympathetic balance, which led to hypertension. Thus, the fact that patients with clinical evidence of hypertensive cardiac failure showed an elevation of the potassium level of the blood, supports the conception that the raised potassium level was the result and not the cause of arterial hypertension.

The eight cases of involved hypertension that showed high potassium values may indeed have had some degree of cardiac failure, because it is well recognized that the evaluation of the cardiac reserve in arterial hypertension often offers considerable difficulty. Frequently, when symptoms of cardiac failure are still absent, the cardiac reserve is already impaired. It is evident from clinical observations that "essential hypertension," "primary arterial hypertension," and "uncomplicated hypertension" are only relative terms and designate but one stage of the disease. A patient who suffers from uncomplicated hypertension may succumb later as a result of cardiac or renal insufficiency. It is therefore probable that several of the cases that did not exhibit clinical evidence of cardiac failure nevertheless had impaired circulatory function which resulted in a rise in the potassium of the serum. Finally, the observation of an elevated potassium content of the blood in cardiac failure without hypertension (Spiro⁶ and Kisch⁸) is weighty evidence against the theory that an increase of potassium in the blood is the cause of arterial hypertension.

Elevation of the blood potassium without hypertension may be due to other causes than an overactivity of the parasympathetic nervous system. But even if one were to concede that in certain instances of uncomplicated hypertension the elevation of the blood potassium is an indication of an overactive parasympathetic system, there is no evidence that such increase of the blood potassium affects the arteriolar resistance and thus the arterial pressure. That, indeed, an elevated level in the blood potassium, as observed in the few cases of essential hypertension, does not increase the blood pressure is substantiated by the observation that there is a high potassium level in the blood of patients with bronchial asthma, gastric ulcer and in certain types of neurosis.⁵⁹

59 Kylin, E. *Die Hypertoniekrankheiten*, Berlin, Julius Springer, 1926, p. 86

An analysis of the literature reveals that the claims that the parasympathetic part of the autonomic nervous system is overactive in arterial hypertension are based on impressions and assumptions rather than on careful analytic observations. There is a tendency to assume that an overactivity of the psychic function is associated with stimulation of the autonomic system, and it is often not appreciated that psychic overactivity and sympathetic overactivity frequently are not in causal relationship and are present alone and not in combination. Moreover, there may be an overactivity of one or more sections of the sympathetic or parasympathetic nervous system with normal functioning of the rest of the system. Dennig, Fischer and Beringer⁶⁰ observed that the responses of the vegetative nervous system do not depend essentially on the psychic state of the patient. Recently, Weiss and Patek⁶¹ made a study of the psychic state and the autonomic nervous system in forty-two patients with arterial hypertension and in thirty-seven control cases. While the patients suffering from hypertension were overexcitable, impulsive and sensitive, the tests applied for the study of the autonomic nervous system failed to prove a definite overactivity of the parasympathetic nervous system.

It has been definitely established by the analyses presented that no change from the normal range occurs in the calcium level of patients with hypertension. The averages for the cases involved and uninvolved hypertension are well within the normal range and compare favorably with normal values obtained by other authors using the same method. That the calcium level of patients with hypertension does not change is indirectly verified by the fact that the inorganic phosphorus level and the calcium-inorganic phosphorus ratio are normal. These results remove any rational basis for the administration of calcium for the elevation of the blood calcium through potent extracts of the parathyroid glands as beneficial therapeutic procedures in arterial hypertension.

Of the thirty-seven patients with uncomplicated hypertension, 54 per cent presumably had hypercholesteremia, and 46 per cent showed normal values. When, however, the records of the patients with hypercholesteremia were examined, it was found that only five of the group had no recorded secondary complications other than hypertension, two patients were recovering from bronchial pneumonia, two suffered from duodenal ulcers, three from cerebral hemorrhages, three had a high nonprotein nitrogen content of the blood and low specific gravity of

60 Dennig, H., Fischer, K., and Beringer, K. *Psyche und vegetatives Nervensystem*, *Deutsches Arch f klin Med* **167** 26, 1930

61 Weiss, S., and Patek, A. J., Jr. Unpublished study

the urine, one was passing through menopause, one had had an oophorectomy, one had tertiary syphilis, and two had cardiac asthma. It has been repeatedly observed⁶² that the cholesterol level often sinks in infections (such as bronchopneumonia) and rises during recovery, that the level rises markedly in most forms of internal bleeding and in renal involvement, and that various changes in the cholesterol level occur in disturbances of the secretions of the gonads. Thus, of thirty-seven patients with uninvolved hypertension, only 13 per cent had a hypercholesteremia that could not be explained on the basis of known complications. Moreover, a too rigid interpretation of cholesterol values is rather hazardous. The cholesterol level in normal people is known to fluctuate as much as 35 mg per hundred cubic centimeters during the course of a month (Muller⁶²). Therefore, a marked deviation of the cholesterol level from the normal range, such as is reported in pernicious anemia and diabetes, must necessarily be present before any definite rôle can be attributed to the cholesterol content of the blood in arterial hypertension. Such an alteration has not been observed. It should be remembered also that although the usual functional tests of the kidneys fail to reveal an impaired renal function, a considerable encroachment on the normal reserve of the kidneys may be present in arterial hypertension. Observations by Weiss and Ellis⁶³ indicate that in essential hypertension the flow of blood through the kidneys, as measured with the urea clearance test, may be considerably reduced although the function of the kidney as measured by other methods is still normal. Thus the slightly elevated cholesterol level observed in a few instances may be the result of early renal involvement.

In attempting to correlate changes in the potassium-calcium ratio to changes in the cholesterol level, it was found that of the twenty presumable cases of hypercholesteremia observed in the patients with involved hypertension, only 25 per cent showed a ratio of over 2.35, of the five cases of hypercholesteremia with no known involvements affecting the cholesterol level, not one showed a high potassium-calcium ratio. Thus in these cases of hypertension, there is definitely no relation between changes in the potassium-calcium ratio and the cholesterol level.

The results of this study, therefore, do not support the hypothesis that increased potassium, increased cholesterol or decreased calcium content of the circulating blood alone or in combination is responsible for the increase in the arteriolar resistance of arterial hypertension. Since the claims that other circulating substances, such as guanidine, the amino-acids, epinephrine and chloride ions, cause arterial hypertension are similarly not supported by reliable, direct observations in man, one

62 Muller, G. L. Personal communications to the authors.

63 Weiss, S., and Ellis, L. B. Unpublished observations.

must conclude that direct experimental support is thus far lacking in the numerous clinical suggestions that a "circulating chemical element" is responsible for increased peripheral resistance, and therefore is the responsible factor in the causation of arterial hypertension

SUMMARY AND CONCLUSIONS

1 A study of the significance of the potassium-calcium ratio and the inorganic phosphorus and cholesterol of the blood serum in seventy-five cases of hypertension and twenty-five control cases is presented

2 The average potassium level rose from 20 to 22.15 mg per hundred cubic centimeters of serum in seventy-five cases of hypertension with or without secondary complications. This rise was most marked in cases of hypertension with cardiac involvement, in which the average level was 22.8 mg per hundred cubic centimeters

3 The average calcium level in seventy-five cases of hypertension with and without complications was normal (9.75 mg per hundred cubic centimeters) as compared with that of the control group (9.8 mg per hundred cubic centimeters)

4 The correctness of the observations on the normal amount of calcium in arterial hypertension was supported by the fact that the inorganic phosphorus level in these seventy-five cases (4.1 mg per hundred cubic centimeters) showed no tendency to increase above the average amount of inorganic phosphorus in the controls (4.3 mg per cent), while the calcium-inorganic phosphorus ratio of the seventy-five cases of hypertension (2.43) showed no tendency to fall below that of the control cases (2.33)

5 The potassium-calcium ratio rose from a control level of 2.05 in twenty-five control cases to 2.32 in seventy-five cases of hypertension with or without involvements. This rise was most marked in patients with hypertension and cardiac involvement (2.38) and least in patients with uninvolved hypertension (2.19)

6 The slight increase observed in the potassium level and in the potassium-calcium ratio observed in the cases of hypertension was probably due to impairment of the circulatory functions

7 The cholesterol level rose from a control level of 171.6 to 204.5 mg per hundred cubic centimeters in seventy-five cases of hypertension with or without involvements. This rise was most marked in patients with hypertension and renal involvement (227 mg per hundred cubic centimeters) and least in patients with hypertension and cardiac involvement (194 mg per hundred cubic centimeters). Of thirty-seven cases of uninvolved hypertension, only five (13 mg per hundred cubic centimeters) showed an unexplainable hypercholesteremia

8 There was no relation between the potassium-calcium ratio and the cholesterol content of the blood in hypertension

9 Neither changes in the potassium-calcium ratio nor hypercholesteremia can be considered as playing a fundamental rôle in the development of arterial hypertension. Elevation of the potassium and cholesterol levels observed in one group of patients with hypertension is the result rather than the cause of changes in the cardiovascular system in arterial hypertension

Dr F H L Taylor advised concerning the selection and adaptation of the chemical methods used in carrying on this investigation

THROMBO-ANGIITIS OBLITERANS (BUERGER)

VI CHEMISTRY OF THE BLOOD¹

MAE FRIEDLANDER, PH D

AND

SAMUEL SILBERT, MD

NEW YORK

In a recently published paper,¹ we stated that there is a striking reduction in the volume of blood in thrombo-angitis obliterans. In order to determine whether this reduced amount of blood is concentrated or normal, we studied the amounts of the individual chemical constituents in the blood. Determinations of the total amount of ash, total amount of proteins, chlorides, calcium, phosphorus, cholesterol, fasting sugar and the tolerance for sugar were made. In a small group of cases the specimens of blood were also subjected to a determination of fractional proteins in order to see whether any striking variation could be discovered.

REVIEW OF THE LITERATURE

A review of the literature on chemical studies of the blood in thrombo-angitis obliterans is not illuminating, for in most instances the number of cases studied was few, and the conclusions drawn do not agree. Various investigators have focused their attention on one or more constituents, but no one has presented a complete chemical picture of the blood in an adequate number of cases. Bernhard² reported that the nonprotein nitrogen, calcium, cholesterol and chlorides were within normal limits and that in a few cases the blood sugar was elevated during fasting. Heitz³ stated that the cholesterol was increased, ranging between 250 and 305 mg per hundred cubic centimeters. Troisier and

* Submitted for publication, Jan 2, 1931

¹ From the Out-Patient Department and the Laboratories of the Mount Sinai Hospital

² This work was aided by a grant from the Samuel Kellar Jacobs Research Fund for Thrombo-Angitis Obliterans

1 Silbert, S, Kornzweig, A L, and Friedlander, M. Studies in Thrombo-Angitis Obliterans (Buerger). IV Reduction of Blood Volume, Arch Int Med **45** 948 (June) 1930

2 Bernhard, Adolph. Summary of the Chemical Blood Findings in Thrombo-Angitis Obliterans, Med Rec **97** 430, 1920

3 Heitz, Jean. De la cholesterinemie chez les sujets affectes d'arteritis obliterantes, Ann de med **14** 378 (Nov) 1923

Ravina⁴ likewise found increased cholesterol, averaging about 240 mg per hundred cubic centimeters. Kuwabara,⁵ quoted by Koyano,⁶ reported normal figures for cholesterol and normal tolerance for sugar in the cases that he studied among the Japanese. Allen and Brown⁷ reported normal figures for blood sugar and urea, and they are the only ones who found figures for cholesterol at the lower limit of normality. Meleney and Miller⁸ studied the content of sugar during fasting and the tolerance for dextrose in 20 cases, and then found no striking variation from normal. Jablons⁹ also found a normal tolerance for dextrose. He quoted Kahn's unpublished studies and stated that in 6 cases the calcium content was increased. Belegorodsky, quoted by Oppel,¹⁰ found an increased content of calcium in the blood in this condition. In a personal communication, Dr. Alice Bernheim stated that she found the calcium level elevated. In his book,¹¹ aside from a reference to Koyano's paper, Buerger did not discuss the chemical constituents of the blood. The preponderance of evidence, therefore, seems to indicate that increased amounts of calcium and cholesterol are present and that the tolerance for sugar is normal.¹²

MATERIAL AND METHODS

The patients investigated had typical cases of thrombo-angitis obliterans, they were selected at random from the large number being treated in the special clinic for this disease in the outpatient department of the Mount Sinai Hospital. The group represented all stages of the disease and various ages, and included both patients to whom treatment had been given and ones who had not received treatment. More than 100 cases were studied, but in order to avoid the inaccuracies that might have been present in the earlier determinations, the data of only the last forty cases are presented. A group of controls were studied to check the accuracy of our technic, and in each instance the figures obtained were within

4 Troisier, J, and Ravina, A. La citrate de soude intraveineux dans la thrombo-angite oblitérantes, *Bull et mem Soc méd d hôp de Paris* **48** 570 (May 15) 1924.

5 Kuwabara, M. Beitrage zur Aetiologie der Spontangangran an den Extremitäten, *Kyoto Igaku Zasshi* **17** 61, 1920.

6 Koyano, K. Clinical Study of 120 Cases of Thrombo-Angitis Obliterans Among the Japanese, *Acta scholae med univ imp, Kyoto* **4**:489, 1922.

7 Allen, E. V., and Brown, G. E. Thrombo-Angitis Obliterans, A Clinical Study of 200 Cases, *Ann Int Med* **1** 535, 1928.

8 Meleney, F. L., and Miller, G. G. Contribution to the Study of Thrombo-Angitis Obliterans, *Ann Surg* **81** 976, 1925.

9 Jablons, B. Thrombo-Angitis Obliterans, *Internat Clin* **3** 193, 1925.

10 Oppel, V. A. Gangrène spontanée et surrénalectomie, *Lyon chir* **24** 1, 1927.

11 Buerger, Leo. The Circulatory Disturbances of the Extremities. Philadelphia, W. B. Saunders Company, 1924.

12 Leibovici, R. Etude chirurgicale des gangrènes juveniles, Paris, Gaston Doin, 1928.

TABLE 1—*Chemical Constituents of the Blood in Forty Cases of Thrombo-Angutis Obliterans*

Name	Date	Blood Volume per Kg, Cc	Total Ash Con- tent in Plasma, Gm per 100 Cc	Total Protein Content in Blood, Gm per 100 Cc	Calcium in Serum, Mg per 100 Cc	Phos- phorus in Serum, Mg per 100 Cc	Chloride in Plasma, Mg per 100 Cc	Choles- terol in Plasma, Mg per 100 Cc
L E	1/31/30			21.5	12.4			265
L C	2/28/30		1.5	22.0	11.0	1.8	52.6	220
J B	2/26/30		1.3		13.0	2.0	59.7	250
M G	3/ 8/30			23.7	12.0	2.0	62.0	235
M H	3/21/30		1.3	20.0	13.0	1.8	58.0	200
	3/25/30		1.4	21.2	12.0	2.0	58.5	185
J W	4/14/30		1.3		11.9	1.9	52.6	210
W B	4/15/30	63.7	1.0	22.5	11.9	2.0	50.0	235
	4/24/30	63.4		23.8	12.8	2.0	50.0	250
	8/25/30		1.2	22.5	12.5	2.0	51.5	250
J G	4/17/30	71.8	1.3		12.0	2.0	52.6	250
M W	5/14/30	46.3	1.7	21.0	12.2	1.8	52.6	220
	5/16/30		1.6	23.0	11.8	2.0	49.2	210
H R	6/17/30		1.0	22.5	11.5	1.8	46.8	210
M P	7/11/30		1.2	21.0	12.0	1.8	52.6	235
	8/ 6/30		1.1	21.9	12.0	2.0	52.6	235
L K	7/15/30			23.1	12.0	2.0	52.6	235
	7/17/30			23.1	12.0	2.0	52.6	235
B B	7/15/30			23.1	12.0		51.5	235
	7/17/30			22.5	12.0	1.8	52.6	265
D S	7/25/30			22.5	12.5	2.0	51.5	235
	7/28/30			23.1	13.0	2.0	52.6	235
D P	7/28/30	68.0		22.5	13.0	1.8	52.6	200
M F	7/28/30	66.0		23.1	13.0	1.8	52.6	250
	7/30/30			23.8	12.0	2.0	51.5	250
R M	8/25/30		1.1	22.5	12.5	2.0	52.6	235
	9/10/30		1.1	22.5	13.0	2.0	51.5	235
J M	8/29/30	65.2	1.2	23.1	13.0	1.8	46.8	265
J W	9/ 5/30	58.0	1.5	24.4	12.5	2.0	52.0	210
H Z	2/10/30	75.0	1.2	23.8	12.0	1.3	58.5	210
F Z	2/10/30		1.2	23.0	11.7	1.2	59.7	210
H L	2/ 3/30	69.0			13.6	1.4	63.1	240
E M	2/24/30	69.8		23.8	12.4	2.5	58.5	250
	8/29/30	65.0	1.2	23.8	12.5	1.9	56.0	265
J S	9/ 8/30	50.0	1.3	23.8	13.0	1.5	55.0	250
N G	2/ 5/30			22.5	11.9	1.7	55.0	230
B F	2/10/30		1.3	20.0	12.8	1.4	58.5	270
	2/28/30		1.2	22.5	12.0	2.0	56.1	220
D K	2/10/30		1.0	20.6	10.8	1.5	59.7	250
	3/17/30		1.3	22.5	11.4		64.0	220
E L J	2/21/30		1.2	22.5	12.0	1.7	64.0	235
A L	2/26/30	58.5	1.0	24.0	12.6	1.9	55.0	210
J S	2/22/30	62.4	1.0	24.0	12.0		58.5	210
	9/ 6/30	52.0	1.3	25.0	13.0	1.8	58.5	220
C K	2/24/30	65.2			12.2	2.0	58.5	195
	9/ 5/30	53.0	1.3	24.4	13.0	2.0	55.0	250
T Z	6/ 4/30	64.8	1.2		11.5	2.0	52.6	250
	8/20/30	54.0	1.3	21.8	12.0	2.0	52.6	250
J F	9/ 8/30	53.0	1.3	23.1	12.0	1.9	50.3	235
H E	3/12/30	68.0	0.9	22.5	12.0	1.8		235
	8/20/30	62.0			12.5	1.8	51.5	210
B L	3/19/30	62.0	1.2	23.4	13.3	2.2	67.8	250
M W	4/ 2/30	53.0	1.2	22.5	11.6	1.9	55.0	250
B R	4/14/30	71.0	1.1	23.0	12.0	2.0	53.8	210
B S	8/14/30		1.3	22.5	13.0	2.0	51.5	265
H G	8/18/30		1.2	23.8	13.0	2.0	52.6	250
B B	8/18/30	56.0	1.2	23.8	14.0	1.8	52.6	265
D L	8/21/30	60.0		23.1	14.0	1.8	56.0	250
Average		61.6	1.2	22.8	12.4	1.9	54.7	235

the accepted range of normal. All of the patients and the subjects used as controls were males. All determinations were made on specimens of blood obtained in the morning before the patient had broken his fast.

The determinations of the total amount of ash were made after evaporating and ashing from 2 to 5 cc of plasma. The total nitrogen content was obtained by the Kjeldahl macroscopic and microscopic methods, and the total protein content was computed by multiplying by 6.25¹³. Determinations of calcium were made by the Clark-Collip modification of the Kramer-Tisdall method¹⁴. To insure com-

TABLE 2—*Chemical Constituents of the Blood in Twenty-One Normal Persons*

Name	Date	Blood Volume per Kg, Cc	Total Ash Con- tent in Plasma, Gm per 100 Cc	Total Protein Content in Blood, Gm per 100 Cc	Calcium in Serum, Mg per 100 Cc	Phos- phorus in Serum, Mg per 100 Cc	Chloride in Plasma, Mg per 100 Cc	Choles- terol in Plasma, Mg per 100 Cc
A F	2/12/30				10.0		41.0	135
B S	2/18/30		0.9	18.8	10.2	1.9	52.6	135
C B	3/ 8/30			15.0	10.6	1.8	46.8	150
S S	3/ 8/30			15.0	10.2	2.0	47.0	185
I M	4/ 9/30			18.8	9.0	2.0	49.1	180
S G	6/ 4/30		1.0	15.0	9.7	2.0	52.6	170
H S	6/ 4/30		1.0	16.8	10.2	2.0	52.6	185
A A	6/12/30		1.0	20.0	10.5	2.8	49.0	185
A K	6/12/30		0.9	15.0	10.1	2.7	47.9	170
W L	6/12/30		1.0	13.5	10.2	2.8	46.8	150
E S	6/12/30		0.9	17.5	10.1	2.8	46.8	170
F K	8/ 4/30		0.9	18.8	8.0	2.8	46.8	165
T N	8/28/30		0.9	18.8	10.0	3.0	52.6	165
Average			0.9	16.9	9.9	2.4	48.6	165
V V*	2/28/30		1.2	18.8	8.4	2.5	46.8	265
G G*	3/12/30			25.0	10.0	2.5	65.0	220
	3/28/30			23.0	11.2	2.0	58.5	270
	8/27/30		1.0	21.3	10.5	2.0	52.6	270
W H*	4/17/30		0.9	18.8	10.9	1.9	56.0	170
D K*	6/19/30		1.0	21.0	10.5	2.0	46.8	265
S U*	7/ 1/30		1.0	23.1	11.0	2.0	51.5	270
H S*	7/ 8/30		1.0	23.1	11.0	2.0	51.5	270
H S*	8/ 4/30		1.0	20.0	11.0	2.5	51.5	250
I G*	8/28/30		1.0	20.0	10.5	3.0	51.2	265
Average			1.0	21.4	10.5	2.2	53.1	250

* These patients were heavy smokers. The high figures for the total protein and cholesterol content are noteworthy.

plete precipitation of the calcium the mixture of serum ammonium oxalate was allowed to stand for twenty-four hours. Studies on phosphorus were made by the Kuttner and Lichtenstein method¹⁵. Figures for cholesterol were obtained by the Sackett modification of Bloor's method¹⁶. Chlorides were studied by the

13 Hawk and Bergeim. *Practical Physiological Chemistry*, ed 9, Philadelphia, P. Blakiston's Son & Company, 1927, p. 711.

14 Clark, E. P., and Collip, J. B. A Study of the Tisdall Method for Determination of Blood Serum Calcium with a Suggested Modification, *J. Biol. Chem.* **63** 461, 1925.

15 Kuttner, T., and Lichtenstein, L. Micro Colorimetric Studies. Estimation of Phosphorus, *J. Biol. Chem.* **86** 671, 1930.

16 Sackett, Guy E. Modification of Bloor's Method for the Determination of Cholesterol, *J. Biol. Chem.* **64** 203, 1925.

method of Van Slyke,¹⁷ and the sugar content, by the modified Folin-Wu method¹⁸ Tests for sugar tolerance were made after the administration of sugar by both the oral and the intravenous method¹⁹

RESULTS

Total Ash Content—The inorganic content of the plasma was determined by evaporating a known amount of plasma in an oven to a dry weight, and then incinerating it until all organic matter was consumed A normal figure for the total ash content is about 0.9 Gm per hundred cubic centimeters, and from 0.8 to 1 Gm may be taken as the limits of normal variations Forty determinations of the total ash content in patients with thrombo-angitis obliterans gave

TABLE 3—*Determination for Fractional Plasma Protein in Ten Persons with Thrombo-Angitis Obliterans and Four Normal Persons*

Patients with Thrombo Angitis Obliterans		Fibrin, per Cent	Albumin, per Cent	Globulin, per Cent
A R		0.48	4.90	2.50
T Z		0.53	5.29	2.29
M K		0.58	4.77	2.69
J B		0.37	5.04	1.82
A S		0.57	4.82	1.99
B S		0.65	6.03	3.38
S R		0.64	5.18	3.08
I G		0.51	5.72	2.31
B R		0.62	5.71	2.76
W Z		0.66	5.94	2.47
Normal Subjects				
Dr G		0.48	5.28	2.18
Dr S		0.37	5.22	2.10
Dr K		0.42	5.22	2.60
Dr S		0.46	5.82	2.48

an average of 1.2 Gm, as compared to 0.9 Gm in ten control subjects Thus the ash content reveals an average increase in mineral constituents of more than 30 per cent Total solids, as determined by dry weight, show a similar increase

Total Protein Content in the Blood—The total amount of nitrogen in the blood was determined by the standard macroscopic and microscopic Kjeldahl methods The total protein content was estimated by multiplying by 6.25 the figure obtained The normal range of total proteins in whole blood has been estimated as being from 15 to 20 Gm per hundred cubic centimeters² In our group of control cases the

¹⁷ Van Slyke, Donald D. Determination of Chlorides in Blood and Tissue, *J Biol Chem* **58** 523, 1923

¹⁸ Folin, Otto and Wu Hsien. A Simplified and Improved Method for Determination of Sugar, *J Biol Chem* **41** 367 1920

¹⁹ Woodvatt, R. T. Timed Intravenous Injections of Glucose at a Lower Rate, *J Biol Chem* **30** 155, 1917

average figure was 169 Gm per hundred cubic centimeters. In the 40 cases of thrombo-angitis obliterans, the range was from 20 to 25 Gm per hundred cubic centimeters. Thus, with an average of 22.8 Gm per hundred cubic centimeters, there is an increase in the total protein content of the blood of approximately 30 per cent. In 10 cases, a fractional protein analysis was made on the plasma. An increase in all constituents was apparent, but it was more striking in the fibrinogen fraction (table 3).

Calcium and Phosphorus—One of the striking alterations that we found in the patients with thrombo-angitis obliterans was the uniform increase in the calcium content of the serum. In the 40 cases reported, this elevation was clearly illustrated (table 1). The average figure obtained in the subjects used as controls was 9.9 mg per hundred cubic centimeters, which agrees with the figures obtained by other investi-

TABLE 4—*Blood Sugar in Fifty-Three Fasting Patients with Thrombo-Angitis Obliterans*

Mg per 100 Cc	Number of Cases
60-69	4
70-79	14
80-89	11
90-99	11
100-110	13
Total	53

gators. In the patients with thrombo-angitis obliterans, the determinations for calcium by the same method ranged from 10.5 to 13 mg, with an average of 12.4 mg per hundred cubic centimeters. Associated with this elevation in the level of calcium was a decrease in the figures for phosphorus (table 1).

Cholesterol—Another consistent alteration noted in the chemical analysis of the blood was an appreciable elevation in the level of cholesterol in the plasma. The figures ranged from 210 to 265 mg, with an average at about 235 mg per hundred cubic centimeters. Determinations made by the same method on normal subjects averaged 165 mg per hundred cubic centimeters.

Chlorides and Sugar—In a few cases the chlorides in the plasma showed a slight increase over the normal (from 45 to 55 mg per hundred cubic centimeters), but for the most part they may be classed as high normal. Studies made on fifty-three fasting patients showed the level for sugar to be normal (table 4). In 37 cases a study of the tolerance for sugar after its administration by mouth was made, and in 14 cases, after the intravenous injection of dextrose, these tests failed to show any striking abnormality.

COMMENT

From a study of the data presented, the general trend is unmistakable. It is readily apparent that the amounts of organic and mineral matter present in the blood are greater than normal, and that they are roughly equivalent to an increase of about 30 per cent over the figures obtained for our control cases. Since our determinations for the volume of blood in patients with thrombo-angitis obliterans reveal a decrease of from 20 to 25 per cent, it can be stated that with this decrease in volume there is a tendency to an increase in density or concentration. This would suggest that a curious process of chronic dehydration is one of the factors present in thrombo-angitis obliterans. A study of the water metabolism in some of our cases (to be published later) shows abnormalities which may throw some light on this point. That concentration is not the only factor is also apparent from the fact that with elevation of the figures for calcium there is a diminution in the phosphorus.

SUMMARY AND CONCLUSIONS

A chemical analysis of the blood of forty patients with thrombo-angitis obliterans was studied to determine the total ash content, total protein content, calcium, phosphorus, chlorides, sugar and the cholesterol content.

Increases in the total ash content, total protein, and in the calcium and cholesterol were noted. No striking abnormalities were found in the determinations for chlorides and sugar. Tests for tolerance of sugar gave normal results.

The conclusion that there is a tendency to concentration of the blood in thrombo-angitis obliterans seems warranted.

CUTANEOUS LESIONS ASSOCIATED WITH A DEFICIENCY IN VITAMIN A IN MAN*

CHESTER N FRAZIER, M D

AND

CH'UAN-K'UEI HU, M D

PEIPING, CHINA

During the winter and spring of 1928 and 1929 many cases of keratomalacia were seen in the hospital of the Peiping Union Medical College. Most of these occurred among Chinese soldiers, garrisoned in villages in the vicinity of Peiping, who had subsisted for various periods of time on inadequate diets, deficient particularly in animal proteins and fats.

In addition to the classic signs of keratomalacia, the majority of these patients manifested certain cutaneous lesions of such uniform character as to suggest their being of more than coincidental significance. This assumption was given further support by the fact that they were analogous histologically to the pathologic changes in the eye and in other tissues of animals and man following deprivation of fat-soluble vitamin A. As a rule the lesions of the skin preceded the appearance of keratomalacia and responded to dietary therapy simultaneously with the ocular lesions, although much more slowly. None of the patients showed signs of beriberi, pellagra or scurvy.

The fifteen cases constituting the material on which this report is based were first studied in the ophthalmologic clinic, where the diagnosis made was typical keratomalacia of from two weeks to three months' duration. In reporting observations on these and earlier cases, Pillat¹ emphasized the identity of the ocular lesions with those found in infants and children under similar conditions of malnutrition. He also called attention to the generalized manifestations of deficiency in vitamin A among these patients, including involvement of the skin. Cutaneous lesions have hitherto not been described in connection with nutritional ophthalmia, although Bloch² observed a dry, shriveled, scaly condition of the skin among infants affected with the disease, and Wilson

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From the Division of Dermatology and Syphilology of the Department of Medicine, Peiping Union Medical College

1 Pillat, A. Does Keratomalacia Exist in Adults? Arch Ophth 2 256 (Sept) and 399 (Oct) 1929

2 Bloch, C E. Ugeskr f læger 79 1516, 1917

and DuBois,³ among others, reported in association with keratomalacia a condition somewhat similar to that not infrequently present in patients with severe malnutrition without signs of xerophthalmia

All fifteen patients of this series were soldiers, with the exception of one, a pedler, and were admitted to the hospital during February, March and April, 1929. Their ages ranged from 19 to 33 years, the majority being in the early part of the second decade. Each gave a history of having lived on a poor and monotonous diet for periods of from six months to one or more years. The diets consisted chiefly of rice, maize, millet, occasionally a poor grade of wheat flour, white cabbage and salted vegetables. Meats, eggs and green vegetables were rarely eaten, a few patients had never had these articles of food, and others had had them not more often than once a month. Usually the quantity of food was sufficient, but there is reason to believe that the diet in many cases was much poorer both in quality and amount than was reported. The better paid officers who were able to supplement the regular ration were not affected by the disease.

In this connection it is well to call attention to the main features of the ordinary Chinese diet. In an extensive study of the food-stuffs utilized in the common diet of several groups of the Chinese middle classes in Peiping, Wu and Wu⁴ have observed that the average diet is adequate in caloric value but below the optimum in proteins and in vitamins A and D, and low in calcium and phosphorus. Vitamins B and C are probably present in adequate amounts. Practically all the fats and oils used for dietary purposes are of vegetable origin, milk, butter and other dairy products are almost never used. It is clear, therefore, that even under ordinary circumstances of civil life, the Chinese dietary is low in vitamin A.

HISTORY OF SYMPTOMS

The natural history of the development of the lesions of the skin was as follows. Several weeks prior to the onset of the ocular symptoms, the skin became dry and slightly rough. Subsequently, spinous papules appeared at the sites of the hair follicles, first involving the anterolateral aspect of the thighs and the posterolateral aspect of the upper part of the forearms. The eruption gradually spread to the extensor surface of both upper and lower extremities, the shoulders and the lower part of the abdomen, and to a less extent to the chest, back and buttocks. In some cases the skin was darker than normal, turning a dull slate color. There was absence of visible sweating, and the

³ Wilson J. R., and DuBois, R. O. Keratomalacia in an Infant with Post-mortem Examination. *Am J Dis Child* 26:431 (Nov.) 1923.

⁴ Wu, H., and Wu, D. L. *Chinese J Physiol Rep*, ser 1, 1928, p 135.

articular folds, which are usually moist, were dry and covered with closely adherent, delicate scales. The normal markings on the surface of the skin were exaggerated in places, giving it a finely wrinkled appearance.

The follicular papules varied in size according to the stage of development and the degree of perifollicular infiltration. The largest were approximately 5 mm in diameter, hemispherical, rather firm and usually deeply pigmented. The hyperpigmentation extended in a narrow zone beyond the base of the lesion. Each papule held in its apex a keratotic plug which in most instances projected above the surface of the lesion as a hard spinous process, or was covered by a loosely adherent scale that bridged the occluded follicular recess. When expressed, the plugs left gaping central craters in the summits of the papules. The eruption was usually abundant and symmetrical, but occasionally the lesions were few and widely scattered, or more rarely, restricted to a single area.

In five cases there was a marked tendency to pustulation, usually on the extremities, leading to the formation of ecthymatous ulcers. Although as a rule there were not over four or five such ulcers, in one case they were so numerous and so sharply formed as to resemble secondary ulcerative syphilids. Cultures of *Staphylococcus aureus* and *Streptococcus hemolyticus* were obtained from the ulcers in several cases. Scabies was a complicating infection in four instances.

Large numbers of conspicuous comedones were present on the face at the sites commonly involved by acne. In one case, that of a patient 28 years of age, these were the only lesions of the skin besides the general xerosis. A few acneiform papules were also distributed over the same areas. Unlike acne, the skin of the face was dry and without any sign of excessive sebaceous secretion. Occasionally it had a puffy appearance suggesting edema.

The hair was dry but otherwise normal. No remarkable changes in the nails were observed, although two patients had slight transverse ridging of a single nail on each hand. Other than a slate-colored pigmentation of the buccal and lingual mucosa in one patient, and a mild atrophic rhinitis in another, the mucous membranes of the oral and nasal cavities showed no visible variation from the normal.

Examination of the nervous system did not reveal any significant abnormality, and there was no instance of cardiovascular disease in this group of cases. Two patients had pulmonary tuberculosis, and three an acute tracheitis or bronchitis. One of the patients with pulmonary tuberculosis was thought also to have tuberculosis of the intestine. This was the only case in which there were gastro-intestinal symptoms.

Ova of *Ascaris* were found in the stools of eight patients, ova of hookworm in five and cysts of *Entameba histolytica* in one. Four of the fifteen patients were apparently free from intestinal parasites.

Chemical and microscopic examination of the urine gave negative results, with the exception of the patient with advanced tuberculosis, whose urine contained a trace of albumin. This patient also had edema of both feet and ankles of two months' duration, and a severe secondary anemia. Four other patients had anemia of moderate degree. The Wassermann and Kahn tests of the blood gave positive results in two cases, neither of which showed active manifestations of syphilis.

RESULTS OF TREATMENT

After admission to the hospital, the patients were observed for periods of from one week to two months. During this time they were fed a well balanced Chinese diet, chiefly vegetarian, to which were added liver, butter and eggs. Cod liver oil was administered daily in quantities of 30 cc. Each patient also received one lemon a day. In order not to modify the cutaneous lesions, no local medication was employed, and baths were restricted to the minimum required for cleanliness.

Under this regimen there was rapid improvement in the keratomalacia, although there was but little restoration of vision in cases of advanced degeneration of the cornea. In the cases in which the patient was under dietary treatment for two weeks or more, moisture of the skin was definitely increased, and in several visible sweating was observed. Ulcerative lesions healed promptly and completely. The keratotic papules decreased in size more slowly, and many of the central cornified plugs were extruded. In the cases in which the eruptive lesions completely disappeared, delicate atrophic scars, surrounded by a zone of brownish pigmentation, remained at the follicular orifices. Two months was the longest period any patient was under observation, which was not sufficient time for the skin to regain its normal appearance and texture.

Histologic examination of the cutaneous lesions in various stages of growth showed the pathologic process to be essentially one of hyperplasia and hyperkeratinization of the epithelium of the epidermis and hair follicles, with associated metaplasia of the epithelium of many of the sweat ducts to the keratinizing type, degeneration of the glandular structures of the skin and infection.

The horny layer was moderately hypertrophied and of homogeneous structure. The mouths of the hair follicles were greatly dilated by dense masses of horny substance arranged in more or less concentric lamellae. These either projected from the follicles or were flush with

the surface and covered by a continuation of the horny layer. Nuclei were not present in any of the cornified cells. Coiled atrophic hairs were found in some of the follicular plugs. In the region of the hair follicles, and in other areas of epithelial hyperplasia, there was a definite increase not only in the amount of intracellular pigment but in the number of pigment-bearing cells. Very few chromatophores were found in the corium.



Fig 1—Area of skin on the thigh showing follicular papules with projecting horny spines and hyperpigmentation

The lower part of the hair follicles was atrophic, and in some places the tip was completely severed from the rest of the follicle by rather dense connective tissue. On the study of serial sections, the detached segments were found to be occasionally cystic and filled with desquamated epithelial cells. Surrounding such follicles, and to a less extent those in which the keratosis was minimal, were fairly well circum-

scribed areas of loose reticular tissue containing lymphocytes, fibroblasts and occasional endothelial cells. Numerous blood capillaries were present in these areas.

In the sections examined no normal pilosebaceous structure was seen, and only a few remnants of sebaceous glands were found in the midst of the inflammatory zones. The mouths of many of the sweat ducts were dilated and occluded by conical masses of keratinous material. In places the epithelial lining of the upper part of the ducts



Fig 2—Same area as that in figure 1, showing residual pigmentation and scars at follicular orifices two months after dietary therapy was commenced. The large scar at the lower part of the picture followed a biopsy wound.

was increased in thickness and was desquamating. The epithelial cells of the tubules were frequently shrunken and irregular, or the lumen of the glands was dilated and the epithelium greatly compressed.

Pustulation occurred primarily in the follicular plugs and from there extended into the perifollicular tissues. The earliest sign of

ulceration was found in the walls of the distended hair follicles. Hemorrhage did not occur about the follicle or elsewhere in the skin.

A comparison of the changes in the skin of these patients with those in the eye and related structures in human and experimental cases of keratomalacia is of particular interest and offers strong presumptive evidence of the specific nature of the cutaneous lesions. In keratomalacia, according to Mori⁵ and others, there is cornification of the conjunctival and corneal epithelium and, in the later stages, hyperplasia of the epithelial cells of these structures. The keratinizing process extends into the ducts of the para-ocular glands, and the acini may undergo complete disintegration with conversion of the gland into a series of cavities lined by stratified epithelium and filled with desquamated cells. There is an accompanying element of infection, which in the terminal stages of the process constitutes a major factor in the production of corneal disintegration.

In a study of the pathologic changes in rats fed on diets deficient in fat-soluble A, Wolbach and Howe⁶ concluded that the specific morbid process is a widespread keratinization and replacement of many different epithelia by stratified keratinizing epithelium, which they observed in various parts of the respiratory and alimentary tracts, in the eyes and para-ocular glands and in the genito-urinary tract. They were of the opinion that the loss of secretory function in various glands throughout the body and the distinctive changes observed in other tissues were due to the mechanical factors consequent to the formation and retention of the desquamated epithelial cells.

From the study of the patients observed in Peiping with respect to the sequence in which the various pathologic changes occurred in the skin, it appears that the primary process was an excessive epithelial keratinization, resulting in the mechanical occlusion of hair follicles and sweat ducts, and in secondary degeneration of the sebaceous and sweat glands. Necrosis was a terminal event presumably dependent on the decreased resistance of the tissues to infection.

Cutaneous lesions essentially identical to those of this series of cases have been described by Nicolau,⁷ Willshire⁸ and others as a manifestation of scurvy. In correlating changes in the tissues with deficiency in a specific vitamin it should be remembered that single dietary faults rarely occur alone, as a diet that is lacking in one factor

5 Mori, S. Primary Changes in the Eyes of Rats Which Result from Deficiency of Fat-Soluble A in Diet, *J. A. M. A.* **79** 197 (July 15) 1922, *Bull. Johns Hopkins Hosp.* **33** 357, 1922.

6 Wolbach, S. B., and Howe, P. R. *J. Exper. Med.* **42** 753, 1925.

7 Nicolau, W. *Ann. de dermat. et syph.* **7** 399, 1918-1919.

8 Willshire, H. *Lancet* **2** 564, 1919.

is generally deficient in others. It is doubtful whether an uncomplicated deficiency disease ever exists in man, and it is only by carefully planned experimental diets that a specific deficiency disease can be produced in animals.

In view of such facts, one may question the justification of assuming any causal relationship between the deficiency of vitamin A in the diets of the patients at Peiping and the cutaneous lesions, nevertheless, the essential changes in the skin, when compared with those produced in experimentally controlled cases of disease due to deficiency in vitamin A were of such nature as to suggest their being a part of this specific syndrome rather than of that produced by deficiency in other vitamins.

CALCIUM AND PHOSPHORUS METABOLISM IN A CASE OF NONTROPICAL SPRUE WITH ASSOCIATED TETANY^{*}

ALEXANDER MARBLE, M D

Medical Resident, Massachusetts General Hospital

AND

WALTER BAUER, M D

BOSTON

During the course of investigations of various disorders of calcium and phosphorus metabolism, we had the opportunity of studying a patient with nontropical sprue complicated by tetany. The association of sprue with tetany is probably not so common as was once supposed. In reviewing the literature, one finds that a number of such cases have been reported. In some of these reports no mention is made of the values of the serum calcium or serum phosphorus. A search of the literature failed to reveal any report bearing on the total calcium and phosphorus metabolism in this disease syndrome. Analysis of the data reported in this case shows why the resultant tetany was secondary to the long-standing diarrhea and not related to parathyroid deficiency.

REPORT OF CASE

History—A man, aged 39, married, a Jewish physician, was admitted to the metabolism ward of the Massachusetts General Hospital on Dec 4, 1928, complaining of diarrhea of three years' duration. The family history revealed nothing of note. The past history showed that for years he had been subject to frequent colds and infections of the upper respiratory tract with symptoms suggesting chronic bronchitis. In late years he had suffered a great deal from chronic sinusitis, with occasional, acute flare-ups. He had never been out of the United States.

The present illness could be traced back as far as eight years before admission. At this time the patient first noted a slight loss of strength and that he became fatigued more readily than normally. Owing to worries about his home and the demands of a scattered medical practice in Chicago, his habits of living, eating, sleeping, etc., were irregular. Three and one-half years before admission he began to lose weight rapidly, and his weight decreased from a normal 150 pounds

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^{*} From the Medical Clinic of the Massachusetts General Hospital and the Department of Medicine of Harvard Medical School.

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to about 130 pounds (from 68 to 59 Kg) During this time, the bowel movements varied from mushy to formed stools

Three years prior to admission he suffered from a sudden onset of watery diarrhea, with as many as twenty stools a day, which, with remissions, persisted until he entered the Massachusetts General Hospital Remissions had been few, incomplete and secured only by complete rest, warm weather and a low intake of fluids The acute exacerbations of diarrhea were usually preceded by acute infections of the upper respiratory tract, chiefly ethmoiditis and maxillary sinusitis Throughout the three years he noted a gradually increasing pallor of the skin and of the mucous membranes, at times there had been moderate edema of the lower extremities For the past year, there had been periods of soreness of the tongue at the time of the acute exacerbations of diarrhea Four months before admission, he suffered from a severe attack of diarrhea following ethmoiditis From this time until admission, a new train of symptoms arose, viz, tetany, polyuria and perversion of taste and appetite He lost weight steadily and became progressively weaker and more emaciated Prior to his stay in this hospital he had been observed in Chicago at the Michael Reese, the North Chicago, the Washington Boulevard, the Presbyterian and the Billings Memorial Hospitals At the Presbyterian Hospital, he was under the care of Dr Wilbur E Post from Nov 29 to Dec 19, 1927 At this time (a year before we saw him) his stools were watery, acid or neutral in reaction, and contained no blood and very little mucus A yeastlike organism was found in both the sputum and the stools The course of the disease was febrile, with cough, sputum and pleuritic pains in the right side of the chest Roentgenograms of the chest suggested a marked degree of bronchiectasis at the base of each lung

About six weeks after his discharge from the Presbyterian Hospital, he entered the Billings Memorial Hospital, where from Jan 28 to Feb 14, 1928, he was on the service of Dr Walter L Palmer Recorded data at this institution included weight, 83 pounds (37.6 Kg), essentially normal temperature, normal urine and 3,280,000 erythrocytes per cubic millimeter On examinations the sputum did not show tubercle bacilli Roentgenograms of the chest showed fibrosis of the right lung, representing "a healed pyogenic process, either an old pneumonia or bronchopneumonia, or an old interlobar pleurisy" A series of roentgenograms of the gastro-intestinal tract did not show any abnormality After discharge, the patient failed to return to the Billings Memorial Hospital for follow-up study until October, 1928 At this time, though he was stronger and heavier, occasional carpopedal spasms had developed Studies of the blood showed the serum calcium to be 5.7 mg per hundred cubic centimeters During the administration of Collip's parathyroid extract and calcium lactate, the value rose to a level of 7.8 mg per hundred cubic centimeters The diagnosis at the time of the patient's discharge from the hospital was probable nontropical sprue

Physical Examination—At the time of entrance to the Massachusetts General Hospital, physical examination showed a pale, emaciated man of slight build, weighing 33 Kg, with sunken eyes, a dry and inelastic skin, a negative Chvostek's sign, a positive Trousseau's sign and occasional carpopedal spasms The tongue protruded in the midline It was smooth, with red, raw-appearing edges Most of the teeth were missing, and those that remained were carious Examination of the chest showed limited expansion of the right lung with diminished excursion of the diaphragm on the right side There were occasional crepitant râles at the base of both lungs, but friction rubs were not heard There was slight pitting edema about both ankles

Laboratory studies showed red blood cells, 2,260,000 white blood cells, 17,300, and hemoglobin (Tallquist), 50 per cent, a blood smear examination was normal except for slight achromia of the red blood corpuscles. The latter were found to be normal in size, averaging 7.8 microns (median figure) in diameter, none was nucleated or stippled. The urine showed a slight trace of albumin, but nothing else that was abnormal. The bowel movements averaged four a day at first, the stools were usually large, light brown, watery or mushy, and were acid in reaction. There was a definite odor of yeast. Microscopically, there was an excess of neutral fat and fatty acid crystals and a moderate number of undigested muscle fibers. The guaiac test at times gave a moderately positive reaction and at other times, a negative reaction. Bacteriologic study of the stools revealed, in addition to yeastlike organisms, a growth of *B. coli*. Direct smear showed that from 20 to 30 per cent of all of the organisms were yeasts. On January 30, the total fat content of the wet stool was 9.38 per cent. The pancreatic ferments were determined by a study of the duodenal juice, though the proteolytic and amylolytic enzymes were found to be normal, lipolytic enzyme activity could not be demonstrated. The method of McClure and his associates¹ was used for the estimation of the activity of the pancreatic ferments. The results of a gastric analysis,

TABLE 1—*Gastric Analysis After Several Weeks of Treatment with Liver*

	Fasting	15 Minutes After Test Meal*	30 Minutes After Test Meal	45 Minutes After Test Meal
Free hydrochloric acid	0	0.0	0	0
Total acid†	4	7.0	9	10
Chlorides‡	41	32.5	48	

* The test meal consisted of 100 cc. of 7 per cent alcohol. 1 cc. (0.5 mg.) of ergamine acid phosphate was administered subcutaneously at the same time.

† Acidity is expressed in cubic centimeters of tenth normal acid per hundred cubic centimeters of gastric contents.

‡ Chlorides are expressed as cubic centimeters of tenth normal per hundred cubic centimeters of gastric contents.

performed on March 15 (several weeks after there had been improvement through liver therapy), are given in table 1.

Chemical studies of the blood showed sugar during fasting, 88 mg., non-protein nitrogen, 26 mg., total protein, 5.94 Gm. per hundred cubic centimeters, and an icteric index of 3. On the morning after admission, the serum calcium was 6.7 mg. and the serum phosphorus 1.28 mg. per hundred cubic centimeters. The sputum, at times moderately abundant, was yellowish, tenacious and blood-streaked. Microscopic examination showed many pus cells and bacteria of various types, but no yeastlike forms or tubercle bacilli were found. Culture of the sputum showed the predominant organisms to be pneumococci.

Roentgen studies showed a diminution of lime salts in the bones, maxillary sinuses that were less radiant than normal and changes in the chest which suggested "encapsulated fluid, probably interlobar on the right side and a chronic pathological process at the right base."

Course—At the time of entry the patient was seriously ill and difficult to manage, therefore, the diet was not kept so constant as in our previous metabolism

1 McClure, C. W., Wetmore, A. S., and Reynolds, L. New Methods for Estimating Enzymatic Activities of Duodenal Contents of Normal Man, *Arch. Int. Med.* 27:706 (June) 1921.

studies² Because of this difficulty, the diet was ordered "as desired," but in general it was semisolid low in fat and high in calcium, phosphorus, protein and vitamins It included a large amount of milk (from 800 to 2,000 cc a day) The intake of calcium per day varied from 0.6 to 4.3 Gm The ratio of calcium to phosphorus in the diet varied from 1.1 to 1.2.1 The intake of fluid varied from 1.9 to 3.8 liters, while the urinary output varied from 1.15 to 2.15 liters per day

Six days after admission, the administration of liver extract (Lilly no 343) was begun in doses of 6 vials a day After twenty-four days, the dose was reduced to 3 vials a day and was so continued until February 16 From this time until late in the summer of 1929, the patient did not receive liver extract, but during this period a small amount of fresh liver was included in the diet The

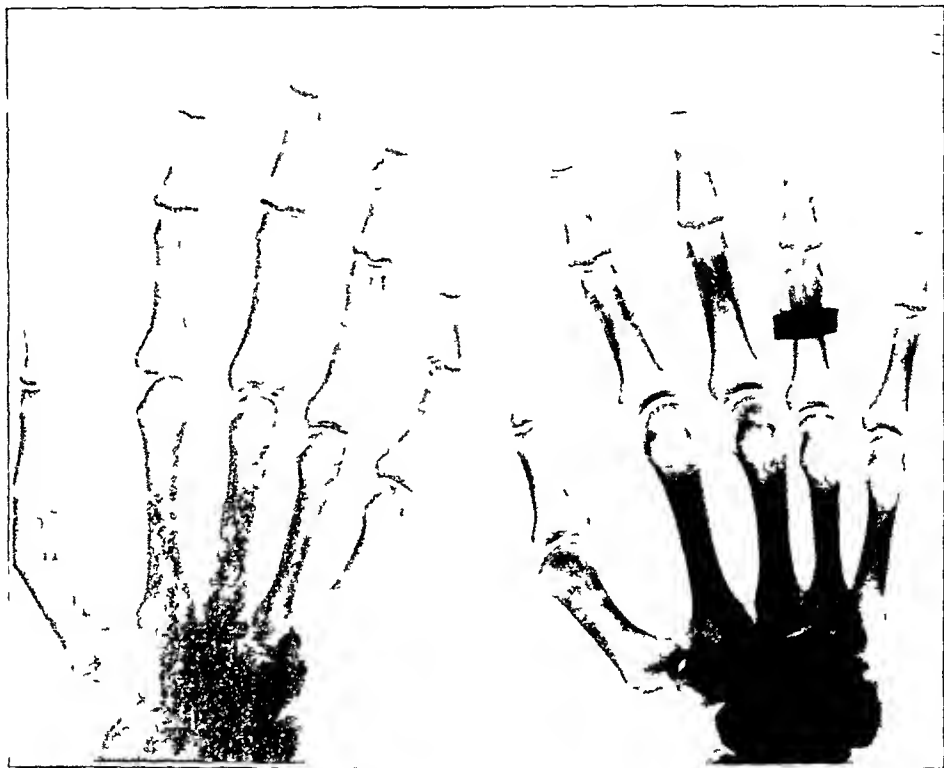


Fig 1—Roentgenogram of the patient's hand (right) as compared with that of a normal person (left) Note the generalized decalcification

administration of iron by mouth was begun on January 2, and increased thereafter, so that from January 24 he received 24 grains (1.56 Gm) of reduced iron a day, and, except for occasional periods, he had continued to take large doses of iron

The most striking index of improvement is to be seen in the curve for body weight (fig 2) Starting at a level of 32.6 Kg on December 4, there was a precipitous rise to the level of 49.8 Kg on January 24 Then followed a period

² Albright, F, and Bauer, W The Action of Sodium Chloride, Ammonium Chloride, and Sodium Bicarbonate on the Total Acid-Base Balance of a Case of Chronic Nephritis with Edema, *J Clin Investigation* 7:465 (Aug) 1929 McClure, Wetmore and Reynolds (footnote 1)

in which there was a loss of weight due to a flare-up in the condition of the chest. Following this there was again a consistent rise until the patient's discharge on March 20, at which time the weight was 50.4 Kg. This continued in the month following discharge, so that when the patient was seen on April 20, his weight was 61.4 Kg.

Coincident with this gain in weight, improvement was evident in other respects. The diarrhea gradually decreased in severity, so that after the patient had been in the hospital for two weeks, he had only one or two bowel movements a day (though the character of the stools changed very little). Further frequency of bowel movements was not noted during his stay in the hospital, except for short exacerbations from February 11 to February 16, and on March 19 and 20, the date of discharge.

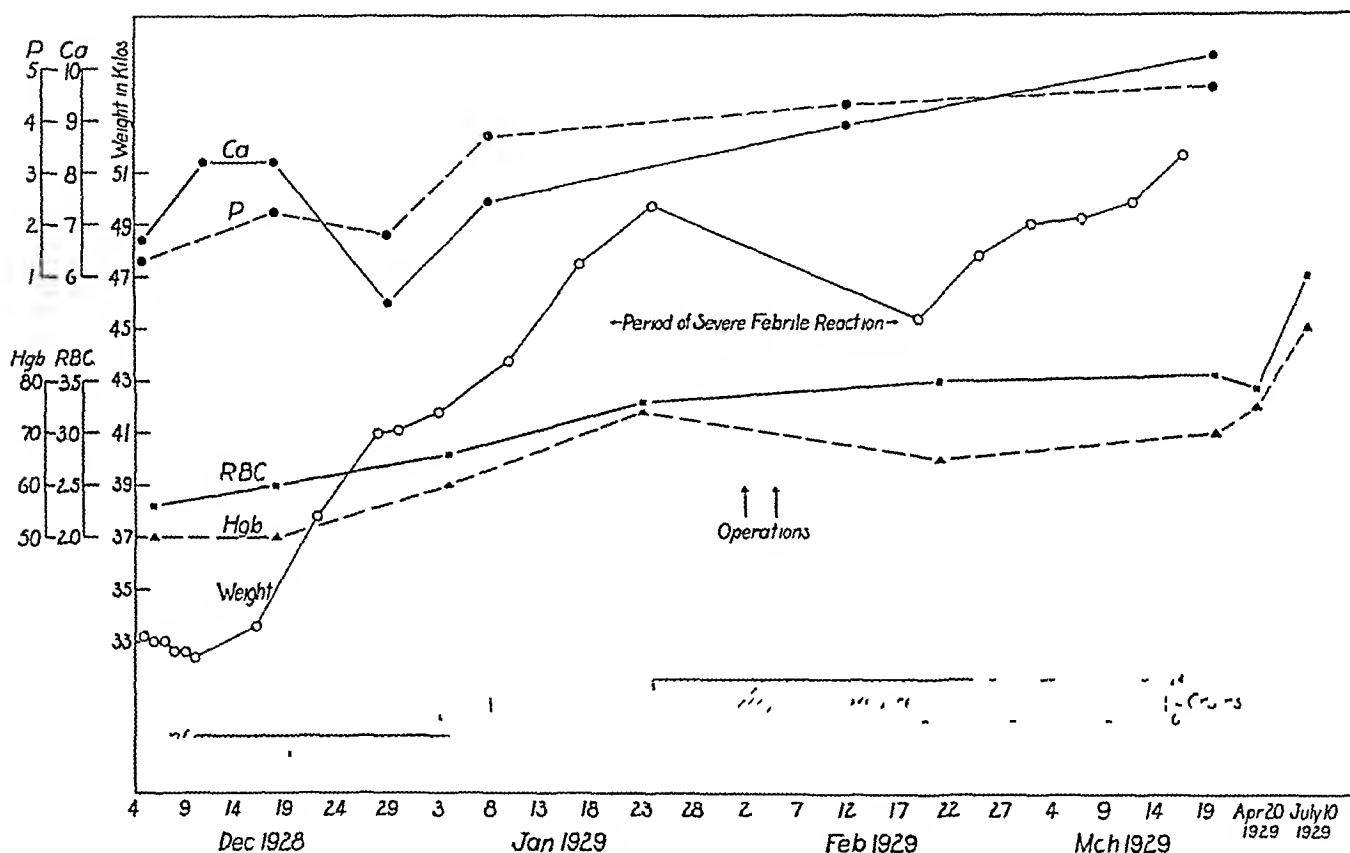


Fig 2—Chart showing the response of the serum calcium, serum phosphorus, erythrocyte count, hemoglobin and body weight to treatment

It is noteworthy that despite the administration of 6 vials of liver extract from December 11 to January 4, during that time the erythrocytes rose only from 2,260,000 to 2,570,000 per cubic millimeter, and the hemoglobin from 50 to 60 per cent. Our data regarding the reticulocyte count during liver therapy are too incomplete to report. By February 21, the erythrocytes and hemoglobin reached a level of 3,500,000 and 70 per cent respectively, and for some weeks could not be raised further despite the administration of liver extract and large doses of iron. However, on July 10, 1929, the erythrocyte count was found to be 4,490,000 and the hemoglobin, 90 per cent. The normal mean diameter of the red cells and the lack of prompt response to treatment with liver extract would place this patient's anemia definitely in the nonmegaloblastic or secondary type. In Ash-

ford's experience, this is unusual, in a recent report,³ he stated that "in this series of anemia sixteen cases have developed during the course of sprue, all but one of these were megaloblastic in type."

Changes in the calcium and phosphorus metabolism will be discussed in detail later in the paper.

On February 3, urinalysis did not reveal abnormalities.

Further comment should be made on the course of the thoracic condition. On January 20, there was a rise in temperature to 101 F. From this time until the condition was relieved a few days later, a septic temperature continued, reaching as high as 104.5 F at times. On January 30, roentgenograms showed a fairly large, encapsulated accumulation of fluid in the lower right interlobar septum, and exploratory puncture was performed. Thick, yellowish-green pus containing pneumococci was obtained. On February 2 resection of a rib was performed by

TABLE 2—Summary of the Condition of the Blood After the Patient's Discharge

Date	Erythrocytes, Millions per Cubic Millimeter	Hemoglobin*	Medication per Day		Comment
			Liver Extract, Vial	Reduced Iron, Grains	
1929					
July 22	4.49	14 Gm per 100 cc			Doing well
Sept 15			1	30	"Health excellent"
Dec 10	2.77	50%	1	30	Occasional transient diarrhea
Dec 15 (about)	3.36	60%	1	30	Occasional transient diarrhea
Dec 18			2	30	
1930					
Jan 3	3.68	60%	2	30	No diarrhea
Jan 16	4.07	75%	2	30	No diarrhea
Feb 4	4.13	65%	2	30	No diarrhea
Feb 21	4.50	70%	2	30	No diarrhea
March 7	4.80		2	30	No diarrhea
March 14	4.83		2	30	No diarrhea
March 25 (about)			2	30	Appendectomy
April 9	4.20		No liver for three weeks	30	No diarrhea
May 31	4.71	85%	Amount unknown (changed to Armour's liquid liver extract)		"Feeling very well (except for numbness and tingling of fingers for 10 days), appetite very good, bowels in excellent shape, lungs not so good as I still have a marked bronchiectasis"

* The Tallquist scale was employed in determining the values for hemoglobin.

Dr. Arthur W. Allen, and on February 5, incision and drainage were carried out. Following this daily saline irrigations of the cavity through a small rubber catheter were instituted. The cavity gradually healed, so that the drainage tube was removed on March 16.

Since discharge from the hospital on March 20, 1929, the patient had reported by letter at frequent intervals. In general, he had done well. He had remained on a diet low in fat, moderate in carbohydrate and high in protein, with as much fruit and vegetables as possible. He had resumed the practice of medicine but had limited his activity. His medication had consisted of liver extract, and (for most of the time) 30 grains (1.95 Gm) of reduced iron a day. He found that 1 vial of liver extract a day was insufficient but that 2 vials were adequate to control the diarrhea. A summary of the observations on the blood is given in table 2.

3 Ashford, B. K. The Anemias of Sprue. Their Nature and Treatment, Arch Int Med 45:647 (May) 1930.

METABOLISM STUDIES

The methods used in the metabolism ward and in the chemical laboratory were those outlined in a previous paper⁴ except that the excreta were collected in six day rather than three day periods as had been our custom in other studies. Calcium was determined by the method of Fiske,⁵ phosphorus by that of Fiske and Subbarow,⁶ total base by that of Fiske⁷ and total nitrogen by the macro-Kjeldahl method.⁸

Calcium and Phosphorus Metabolism—In table 3 and figures 3 and 4 are given the data of the calcium, phosphorus and nitrogen balance and of the serum calcium and phosphorus.

One notes that this patient's diet was adequate⁹ in respect to both calcium and phosphorus during period I (six days), yet the calcium and phosphorus balances were only slightly positive. The fecal values were approximately those of the intake in each instance (the intake of phosphorus was 4.48 Gm and the fecal phosphorus, 4.07 Gm, whereas the intake of calcium was 3.72 Gm, and the fecal calcium, 3.59 Gm). It is shown that the urinary values were extremely low, the urinary phosphorus being 0.21 and the urinary calcium 0.07 Gm. Fecal values of this magnitude must be interpreted as indicating difficulty in intestinal absorption. The low urinary values can easily be accounted for because of the existing low values for serum calcium and phosphorus. It has been well demonstrated that the serum calcium varies as the serum protein varies.¹⁰ The lowered serum protein in this case would account for only a small part of the total reduction in the serum calcium.

The following observations enabled us to differentiate this case of tetany from one due to parathyroid deficiency: a low value for serum calcium (6.7 mg) and serum phosphorus (1.28 mg per hundred cubic centimeters), increased excretion of fecal calcium and phosphorus, decreased excretion of urinary calcium and phosphorus and decreased

4 Bauer, W., and Aub, J. C. Studies of Inorganic Salt Metabolism. I. The Ward Routine and Methods, *J. Am. Dietet. A.* **3** 106 (Sept.) 1927.

5 Fiske, C. H. Method for Calcium Determination (unpublished).

6 Fiske, C. H., and Subbarow, Y. The Colorimetric Determination of Phosphorus, *J. Biol. Chem.* **66** 375 (Dec.) 1925.

7 Fiske, C. H. A Method for the Estimation of Total Base in Urine, *J. Biol. Chem.* **51** 55 (March) 1922.

8 Hawk, P. B., and Bergheim, O. Practical Physiological Chemistry, Philadelphia, P. Blakiston's Son and Company, 1926, pp. 711 and 713.

9 Ashford, B. K., and Hernandez, L. G. Blood-Serum Calcium in Sprue and Other Pathologic States in the Tropics, *Am. J. M. Sc.* **171** 575 (April) 1926.

10 Salvesen, H. A., and Linder, G. C. Observations on the Inorganic Bases and Phosphates in Relation to the Protein of Blood and Other Body Fluids in Bright's Disease and in Heart Failure, *J. Biol. Chem.* **58** 617, 1923. Peters, J. P. and Eiserson, L. The Influence of Protein and Inorganic Phosphorus on Serum Calcium, *J. Biol. Chem.* **84** 155 (Oct.) 1929. Albright and Bauer (footnote 2).

density of bone as determined by roentgen examination Hypoparathyroidism, on the other hand, is characterized by a low value for serum calcium, a high value for serum phosphorus, normal excretion of fecal calcium and phosphorus, decreased excretion of urinary calcium and phosphorus and normal density of bone Therefore, the metabolism data from period I enabled us to state definitely that the tetany in this case was not due to parathyroid deficiency

TABLE 3—Results of Studies of Phosphorus,

Period	Date	Total Fluid Intake, Liters	Total Urine, Liters	Dried Feces, Gm	Phosphorus						Calcium				
					Output			Intake, Gm	Actual Balance, Gm	Theoretical Bal- ance, Gm	Output			Intake, Gm	Balance, Gm
					Urine, Gm	Feces, Gm	Total, Gm				Urine, Gm	Feces, Gm	Total, Gm		
I	1928 Dec 5	17.7	9.5	833	0.20	4.07	4.27	4.43	+ 0.21	+ 0.51	0.07	3.59	3.66	3.72	+ 0.06
II	11	22.6	15.2	335	0.49	1.83	2.32	7.77	+ 5.45	+ 3.80	0.38	2.51	2.89	8.20	+ 5.31
III	17	22.8	15.1	150	0.30	6.84	7.14	15.17	+ 8.03	+ 7.20	0.44	8.54	8.98	17.34	+ 8.36
IV	23	17.7	12.2	162	0.08	5.33	5.41	20.92	+15.51	+11.61	0.11	8.06	8.17	22.43	+14.26
V	29	14.8	11.1	160	0.00	8.51	8.51	19.64	+11.13	+ 9.37	0.06	10.20	10.26	21.14	+10.83
VI	1929 Jan 4	18.3	14.9	191	0.27	8.36	8.63	23.31	+14.68	+12.44	0.05	7.92	7.97	24.41	+16.44
VII	10	18.8	14.9	149	2.95	8.34	11.29	23.24	+11.95	+ 9.64	0.16	11.34	11.50	23.88	+12.38
VIII	16	17.5	12.8	156	3.18	7.66	10.84	25.05	+14.21	+11.43	0.83	8.24	9.07	25.83	+16.76
IX	22	15.8	12.9	251	4.90	13.22	18.12	22.34	+ 4.22	+ 5.16	1.22	17.58	18.80	23.13	+ 4.33
X	28	11.5	6.9	156	5.32	7.14	12.46	11.61	- 0.85	+ 1.90	0.75	8.44	9.19	12.76	+ 3.57

During period II and throughout the remainder of the study, the patient was given liver extract, 6 vials a day from periods II to V, and 3 vials a day from periods VI to X. The clinical improvement that was seen coincident with the administration of liver extract and later with the administration of large doses of inorganic iron (from periods VI to X) has already been commented on in the case report.

Parallel with this improvement in well-being, striking changes occurred in the calcium and phosphorus metabolism. With the administration of liver extract, the diarrhea improved. As a result of such improvement, the excretion of fecal calcium and phosphorus was greatly reduced (relative to the intake) and the urinary calcium and phosphorus

rose, though to a less extent (periods II and III, table 3 and figs 3 and 4) The net result of these changes was a great retention of both calcium and phosphorus, as evidenced by total phosphorus balances of +5.45 Gm and +8.03 Gm and total calcium balances of +5.31 Gm and +8.36 Gm during periods II and III respectively At the same time, the serum calcium rose from 6.7 to 8.2 Mg per hundred cubic centimeters (seventh day of therapy) The serum phosphorus rose

Calcium and Nitrogen Metabolisms

Nitrogen					Total Caloric Intake	Blood Serum				Body Weight		Red Blood Cells	White Blood Cells	Hemoglobin	Treatment		
Output			Intake, Gm	Balance, Gm		In Mg per 100 Cc			Date	Kg	Date				Liver Extract Daily Dose, Vials	Reduced Iron per 5th Day Period, Gm	
Urine, Gm	Feces, Gm	Total, Gm				Calcium	Phosphorus	Total Base									
11.2	13.4	24.6	33.0	+ 8.4	9,683	1928 Dec 5	6.7	1.28	124	1928 Dec 5	33.2	1928 Dec 6	2.26	17.3	50	None	
14.3	14.2	28.5	54.4	+25.9	12,145	11	8.2	4.15		16	33.7					6	
30.4	11.1	41.5	103.5	+62.0	18,535	18	8.2	2.25		22	37.8					6	
36.0	3.6	39.6	133.8	+94.2	22,579					28	41.0					6	
41.3	7.1	48.4	120.1	+80.7	21,477	20	5.5	1.83								6	
55.9	10.6	66.5	158.5	+92.0	26,900	1929 Jan 8	7.5	3.74		1929 Jan 3	41.8	1929 Jan 4	2.57	18.7	60	3	3.01
82.4	5.5	87.9	162.1	+74.2	28,371					10	43.8					3	6.14
101.7	6.5	108.2	180.3	+72.1	30,093					17	47.5					3	6.14
98.7	2.9	101.6	158.7	+57.1	25,710					24	49.7	23	3.36	15.9	72	3	8.19
77.0	3.2	80.2	86.2	+ 6.0	16,377											3	9.22
						Feb 12	8.9	4.30	144	Feb 19	45.4	Feb 21	3.50	12.0	65		
						March 20	10.2	4.57	153	March 2	49.0	March 20	3.56	9.8	70		
										12	49.8	April 20	3.43	15.7	75		
										17	51.6	July 10	4.49	6.8	90		
										April 20	61.4						

from 1.28 to 4.15 mg (seventh day of therapy), but had fallen to 2.25 mg by the fourteenth day. The fall in the serum phosphorus on the fourteenth day of therapy was likely related to the marked gain in weight (4 Kg). Much of the phosphorus retained was probably used to restore the phosphorus content of the replaced interstitial fluid as well as in the building of active protoplasm (see fixed base metabolism). That this gain in weight of 4 Kg was due largely to the restoration of water previously lost is evidenced by the fact that the retention of nitrogen itself was not sufficient to account for the gain in weight.

In periods IV, V and VI the previously noted increased absorption of calcium and phosphorus from the gastro-intestinal tract continued

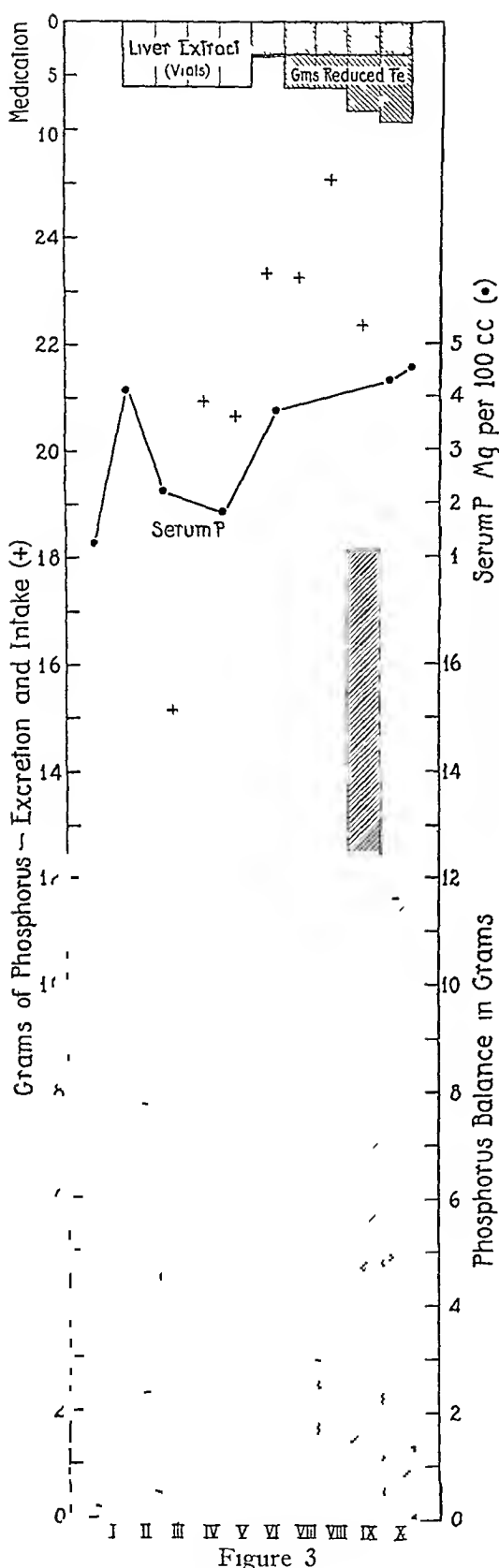


Figure 3

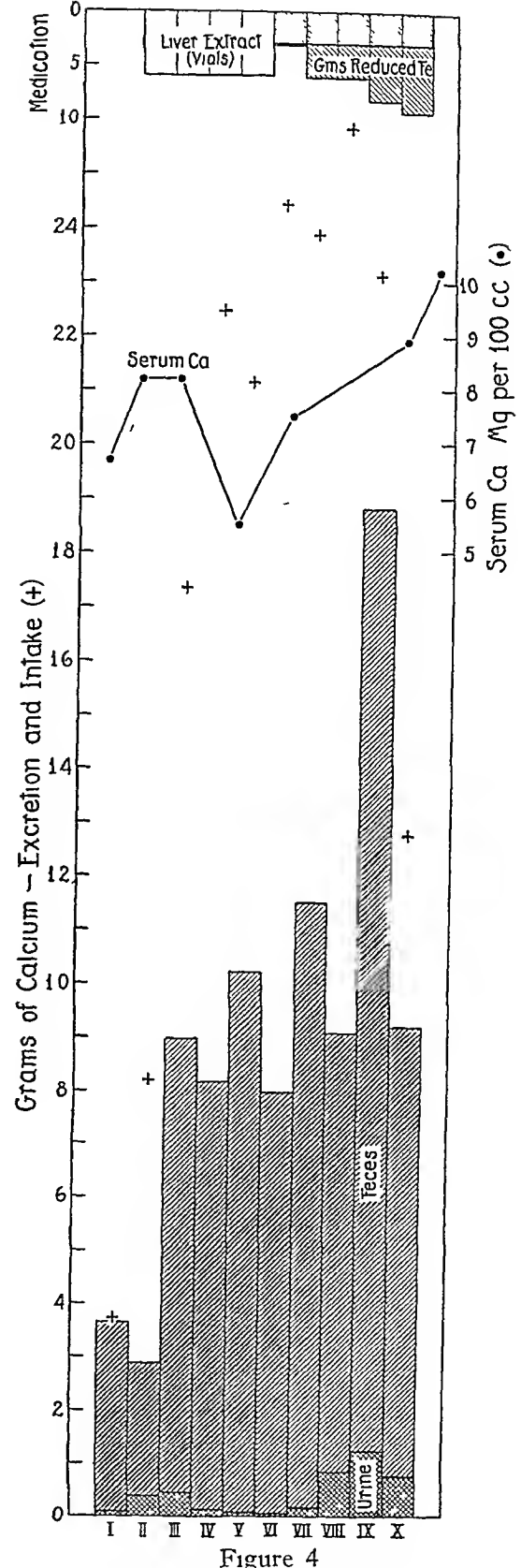


Figure 4

Fig 3—Graphic representation of phosphorus metabolism, the data for which are given in table 3

Fig 4—Graphic representation of calcium metabolism, the data for which are given in table 3

However, the excretions of urinary phosphorus and calcium were much lower than they had been in periods II and III. During period V, the excretion of urinary phosphorus was so low that it could not be estimated by the method employed. During the same period, the urinary calcium was 0.060 Gm., or 10 mg. per day. Interestingly, during this period, the values for the serum calcium and phosphorus were very low (the serum calcium being 5.5 mg. and the serum phosphorus 1.83 mg. per hundred cubic centimeters). In period VI, the urinary phosphorus was increased (0.27 Gm.), but the urinary calcium remained low (0.05 Gm.), approximately 8 mg. a day. However, the serum calcium increased to 7.5 mg., and the serum phosphorus to 3.74 mg. Despite these low values for the urine and serum, a large amount of calcium and phosphorus was retained during periods IV, V and VI. For example, during period VI, the balance of phosphorus was positive to the extent of 14.68 Gm. and the balance of calcium to the extent of 16.4 Gm.

In period V, the low value for serum calcium and the further reduction of the serum phosphorus were probably the result of the deposition of calcium and phosphorus in bone and the establishment of the normal concentration of these substances in the interstitial fluid. Once the latter was accomplished, the increased retention of calcium and phosphorus was reflected in the blood, with elevation of both the serum calcium and phosphorus (period VI, during which the serum calcium was 7.5 mg. and the serum phosphorus was 3.75 mg. per hundred cubic centimeters).

Period VIII represents an advance toward the normal state, with continued high calcium and phosphorus balances. In period IX, there was an increase in the fecal calcium and phosphorus, this is accounted for by an increase in the intestinal rate (note the increase in the weight of the feces, table 3). This was present to some extent in period X, as is shown by the high excretion of fecal calcium and phosphorus (relative to the intake). The gradually increased excretion of urinary phosphorus and decreasing positive nitrogen balance were the result of the increased destruction of protein associated with the interlobar empyema and hyperpyrexia. The loss of weight during this period is further evidence of the increased destruction of protein.

Metabolism of Fixed Base—On the first day of period I, the serum total base was found to be 124 mg. per hundred cubic centimeters (this determination was done in duplicate, and the two results checked extremely well). We believe that this is as low a serum total base as has ever been reported. This value for serum total base was consistent with the severe dehydration present on the patient's entrance to the

hospital Other workers ¹¹ have adequately demonstrated that severe dehydration associated with diarrhea is due to a loss of water and electrolytes from the intercellular fluid This loss of water and electrolytes is not reflected in the blood plasma until the intercellular fluid has been almost depleted If the diarrhea continues sufficiently long, an actual reduction in the plasma electrolytes results and the volume of plasma may be reduced one-third (Detailed studies of this nature were not undertaken because the patient was so acutely ill) It is interesting that with the improvement of the diarrhea a rapid gain in weight resulted This gain in weight during periods II to VI was far greater than could ever be accounted for by the increased positive nitrogen balance It must therefore be interpreted as due to the replacement of the water and electrolytes of the plasma and intercellular fluid This replacement was secondary to the more complete absorption and

TABLE 4—*Comparison of Actual and Calculated Phosphorus Balances*

Period	Phosphorus Balances			Actual, Gm
	Theoretical, Calculated from Calcium Balance, Gm	Theoretical, Calculated from Nitrogen Balance, Gm	Total Theoretical Balance, Gm	
I	0 026	0 48	+ 0 51	+ 0 21
II	2 510	1 49	+ 3 80	+ 5 45
III	3 630	3 57	+ 7 20	+ 8 03
IV	6 200	5 41	+11 61	+15 51
V	4 730	4 64	+ 9 37	+11 13
VI	7 150	5 29	+12 44	+14 68
VII	5 980	4 26	+ 9 64	+11 95
VIII	7 290	4 14	+11 43	+14 21
IX	1 880	3 28	+ 5 16	+ 1 22
X	1 550	0 35	+ 1 90	- 0 85

the decreased excretion which followed the restoration of a normal intestinal rate With these resultant changes, the serum total base gradually approached normal

Comparison of the Actual and Calculated Phosphorus Balances—In table 4 the data on the phosphorus balances are presented in a form which makes possible the comparison of the "theoretical" or calculated phosphorus balance with the actual or determined phosphorus balance The method employed in making such calculations has previously been reported ¹²

The results show that the actual and calculated phosphorus balance in period I agree very well From here on one notes that less phosphorus

11 Hartman, A F Chemical Changes Occurring in the Body as the Result of Certain Diseases, *Am J Dis Child* **35** 557 (April) 1928 Salvesen and Linder (footnote 10, first reference)

12 Albright, F, Bauer, W, Ropes, M, and Aub, J C Studies of Calcium and Phosphorus Metabolism IV The Effect of the Parathyroid Hormone, *J Clin Investigation* **7** 139 (April) 1929

is excreted than was expected according to the calculated phosphorus balance. These differences can probably be accounted for by the replacement of interstitial fluid substances. In period IX, the increased intestinal rate resulted in a greater excretion of phosphorus than would have been expected from the calculated balance. The period X, the actual phosphorus balance was negative, whereas the theoretical phosphorus balance was positive. This difference was due to the increased destruction of protein.

Nitrogen Metabolism—Period I (table 3) shows that nitrogen balance was barely present, (+ 8.4 Gm) before therapy was started. Subsequent to the improvement in the diarrhea, the positive nitrogen balances increased, reaching + 94.2 Gm in period IV. With a tendency of the diarrhea to return, added to the increased destruction of protein, the positive nitrogen balance decreased, so that in period X it was only + 6.2 Gm.

COMMENT

A consideration of the symptoms, clinical course and laboratory studies as outlined leaves little doubt as to the correctness of the diagnosis. The history of recurring attacks of diarrhea, sore tongue, anemia, extreme cachexia and irritability, together with the large, bulky, watery, foamy, light-colored stools, possessing a characteristic yeasty odor, is in accord with the clinical picture of sprue, even though the patient had always lived in the northern part of the United States. It is somewhat difficult to formulate possible causative factors in this case, although the patient's present unusual dietary whims suggest a probably unbalanced and deficient diet in the past. His developmental state suggests that constitutionally his resistance to any chronic disease had probably always been low.

Although in most reports tetany is not stressed as a complication of sprue, a review of the literature reveals a number of such cases. Frequently, note is made of the occurrence of cramps in the extremities, some of these reports undoubtedly represent instances of tetany, although unrecognized as such by the examiner. In 1913, Cantlie¹³ mentioned having seen six cases of tetany with generalized spasms and marked anemia in patients with sprue of long duration. He considered that "these attacks do not imply a fatal issue to the malady." He did not, however, report values for blood calcium. Harrison¹⁴ saw one case of sprue with marked tetany. In 1919, Bassett-Smith¹⁵ reported

¹³ Cantlie, J. Some Recent Observations on Sprue, *Brit. M. J.* **2**: 196 (Nov. 15) 1913.

¹⁴ Harrison, W. S., in discussion on Cantlie, *Brit. M. J.* **2**: 1296, 1913.

¹⁵ Bassett-Smith, P. W. A Case of Sprue Associated with Tetany, *Lancet* **1**: 178 (Feb. 1) 1919.

a case of tropical sprue complicated by tetany in the terminal stage of the disease. Values for blood calcium were not recorded. Bovaird¹⁶ reported two cases of sprue with tetany, one of which had been described by Barach and Murray.¹⁷ One of Bovaird's patients had a serum calcium which varied from 6.5 to 8 mg per hundred cubic centimeters, the other had values from 6.6 to 7 mg.

In 1923, Blumgart¹⁸ reported three fatal adult cases in which there was gradual progressive weakness and emaciation over a period of months, with loose, fatty, bowel movements, achlorhydria and anemia. Two of the three cases exhibited tetany, and in one values for serum calcium of 5.3 mg and for phosphorus of 2.6 mg per hundred cubic centimeters were recorded. In all three cases, postmortem examination showed collections of fat-laden phagocytes in the mesenteric lymph nodes and the mucosa of the small intestine. Blumgart did not regard his cases as characteristic of sprue.

In 1923, Scott¹⁹ reported tetany in a case of sprue and mentioned having seen this complication in many other cases. He observed improvement in such cases with the use of calcium lactate and parathyroid extract by mouth and believed that parathyroid deficiency was intimately concerned with the lowered values for serum calcium and the tetany. All figures for "total" serum calcium quoted in Scott's paper, however, are normal values, his distinction between free and combined calcium is not justified in the light of present knowledge.

One of Jamieson's²⁰ patients had tetany, as did the one in Thaysen's²¹ series, case 8. Neither observer reported values for serum calcium.

In 1926, in Porto Rico, Ashford and Hernández⁹ reported the results of a study of the serum calcium in sprue and in other chronic diseases. In one group of twenty-eight cases, they found values ranging from 7.2 to 10.8 mg, with fifteen instances of a value below 9 mg (the average value given by them for normal healthy controls was 9.6 mg per hundred cubic centimeters). However, critical study of their figures

16 Bovaird, D. A Study of Tropical Sprue, or Psilosis, *J A M A* **77** 753 (Sept. 3) 1921.

17 Barach, A. L., and Murray, H. A., Jr. Tetany in a Case of Sprue, *J A M A* **74** 786 (March 20) 1920.

18 Blumgart, H. L. Three Fatal Adult Cases of Malabsorption of Fat With Emaciation and Anemia, and in Two Acidosis and Tetany, *Arch Int Med* **32** 113 (July) 1923.

19 Scott, H. H. The Nature and Treatment of Sprue, *Brit M J* **2** 1135 (Dec. 15) 1923.

20 Jamieson, T. H. The Treatment of Sprue, *Brit M J* **2** 462 (Sept. 15) 1923.

21 Thaysen, T. E. H. Ueber Fettstarrh  nen. III. Die Klinik der nicht-tropischen Sprue, *Acta med Scandinav* **64** 352 (Sept.) 1926.

reveals that little correlation existed between the clinical severity of the disease and the level of the serum calcium. Indeed, in one series of fifty-five cases, five of the eight "mild" cases and four of the six "moderately severe" cases had values for serum calcium below 9 mg, while only seven of the twenty-one "severe" cases and only nine of the nineteen cases with cachexia had values for calcium below 9 mg. Further, they found that low values for serum calcium were obtained in conditions of malnutrition other than sprue (mention is not made of the concentration of the serum protein¹⁰). Determinations of the serum phosphorus were not made in any of their cases. They, as well as Scott,¹⁹ questioned whether or not in sprue or in the other conditions studied parathyroid deficiency might be considered as the basis of the low values obtained.

Baumgartner and Smith,²² in a study of fifteen cases of sprue, found eight patients with values for serum calcium below 9 mg per hundred cubic centimeters, three of them showed positive Chvostek and Trousseau signs.

More recently, Holmes and Starr²³ reported a series of five cases in which the clinical course bore a striking similarity to the one outlined in this paper. All of their patients had low values for serum calcium, and at one time or another four of the five had active tetany. The authors obtained great improvement with the administration of calcium lactate and Collip's parathyroid extract.

A rise in the serum calcium and relief from tetany were experienced by our patient when Collip's parathormone was administered. However, the fact that tetany associated with sprue is benefited by the administration of an active parathyroid extract is anything but proof that either the sprue or the tetany is related to parathyroid deficiency. The elevation of the serum calcium following the administration of a potent parathyroid extract is due to the ability of this agent to mobilize calcium and phosphorus from bone. This indicates that parathyroid extract should be used only as a temporary expedient to alleviate the tetany. Diarrhea is not a symptom of parathyroid deficiency. Parathyroid deficiency, as has been stated before, is characterized by a low value for serum calcium, a high value for serum phosphorus, normal excretion of fecal calcium and phosphorus, decreased excretion of urinary calcium and phosphorus and normal density of bone. Cases of tetany such as the one reported are characterized by a low value for serum calcium, a low value for serum phosphorus, increased excre-

22 Baumgartner, E. A., and Smith, G. D. Pernicious Anemia and Tropical Sprue, *Arch. Int. Med.* **40**: 203 (Aug.) 1927.

23 Holmes, W. H., and Starr, P. A Nutritional Disturbance in Adults Resembling Celiac Disease and Sprue. Emaciation, Anemia, Tetany, Chronic Diarrhea and Malabsorption of Fat. *J. A. M. A.* **92**: 975 (March 23) 1929.

tion of fecal calcium and phosphorus, decreased excretion of urinary calcium and phosphorus and decreased density of bone Tetany is a syndrome and not a disease entity Its causes are many Parathyroid deficiency is only one of the many conditions that produce tetany Any condition that hinders the absorption of calcium and phosphorus from the gastro-intestinal tract in the amounts necessary to meet the requirements of the body might eventually result in tetany Some of these conditions are (1) dietary insufficiency of either calcium or phosphorus,²⁴ (2) deficiency in vitamin D,²⁵ (3) diets containing a great excess of calcium over phosphorus, or vice versa,²⁶ (4) long-standing diarrhea,²⁷ (5) any disease hindering absorption from the gastro-intestinal tract,²⁸ (6) long-standing biliary or intestinal fistulas²⁹ and (7) excessive excretion of fat³⁰

If any of these conditions persisted, the patient would eventually suffer from deficiency in calcium If the deficiency in calcium remained uncorrected, tetany would ultimately develop The calcium and phosphorus stored in the bone would suffice for the needs of the body for a time, thus preventing the earlier onset of tetany

The patient in the case reported had suffered from diarrhea for three years, and intermittently during the preceding five years He had

24 Maxwell, J P Osteomalacia in China, *J Obst & Gynec Brit Emp* **32** 1, 1925 Hess, A F, and Lewis, J M Clinical Experience with Irradiated Ergosterol, *J A M A* **91** 783 (Sept 15) 1928 Hess, A F Rickets Including Osteomalacia and Tetany, Philadelphia, Lea & Febiger, 1929

25 Steenbock H, and Nelson, M T Fat-Soluble Vitamins XIX Induction of Calcifying Properties in a Rickets-Producing Ration by Radiant Energy, *J Biol Chem* **62** 209, 1924 Hess and Lewis (footnote 24, second reference)

26 Karelitz, S, and Shohl, A T Rickets in Rats II The Effect of Phosphate Added to the Diet of Ricketic Rats, *J Biol Chem* **73** 665 (June) 1927 Orr, W J, Holt, L E, Jr, Wilkins, L, and Boone, F H The Relation of Calcium and Phosphorus in the Diet to the Absorption of These Elements from the Intestine *Am J Dis Child* **28** 574 (Nov) 1924

27 Linder G C, and Harris, C F Calcium and Phosphorus Metabolism in Chronic Diarrhea with Tetany, *Quart J Med* **23** 195 (Jan) 1930

28 Parsons, L G Bone Changes in Renal and Celiac Infantilis, *Arch Dis Child* **2** 1 (Feb) and 198 (Aug) 1927

29 Tammann, H Ueber die Beeinflussung der porotischen Osteomalazie nach Gallenistel durch das D-Vitamin, *Beitr z klin Chir* **142** 83, 1928 Dieterich, H Die porotische Malazie nach Gallenisteln, *Beitr z klin Chir* **134** 530, 1925 Seifert, E Zur Frage der porotischen Malazie nach Gallenisteln, *Beitr z klin Chir* **136** 496, 1926 Duttman, G Die Veränderung des Saure-Basengleichgewichtes nach Gallenisteln und ihre Bedeutung bei der Entstehung der sogenannten porotischen Malazie, *Beitr z klin Chir* **139** 720, 1927

30 Telfer, S V Studies in Calcium and Phosphorus Metabolism IV The Influence of Free Fatty Acids in the Intestine on the Absorption and Excretion of the Mineral Elements, *Quart J Med* **20** 1, 1926, V Infantile Rickets, The Excretion and Absorption of the Mineral Elements and the Influence of Fats in the Diet on Mineral Absorption, *ibid*, p 7

achlorhydria and a complete absence of lipolytic enzyme activity. Both of these abnormalities are known to cause diarrhea. Achlorhydria and decreased pancreatic enzyme activity are not uncommon in sprue.³¹ Besides the diarrhea in this case, there are two other factors that might conceivably interfere with the absorption of calcium and phosphorus, namely, achlorhydria and the absence of lipolytic enzyme activity. The effect of the achlorhydria on the absorption of calcium and phosphorus cannot be stated with any degree of certainty, but it is generally accepted that lowered intestinal acidity hinders such absorption.³² The increased excretion of fat (due to the absence of lipolytic enzyme activity) has been shown to result in the formation of insoluble calcium soaps, which are subsequently excreted.

The facts that the excretion of fecal calcium and phosphorus almost equalled the intake of these substances and that these fecal values decreased following the improvement of the diarrhea would seem sufficient evidence that the tetany in this case resulted from faulty absorption secondary to the diarrhea. Various workers have demonstrated that sprue, like pernicious anemia, is also a deficiency disease.³³

It would be interesting to speculate as to what effect a concentrated preparation of vitamin D would have had on this patient. However, if his condition was in any way related to a deficiency in vitamin D, this lack was not corrected materially by the administration of liver extract because the content of vitamin D in such preparations is extremely low. Presumably, an increased absorption of vitamin D might have resulted in the improvement of the diarrhea.

SUMMARY

1 Studies of the calcium and phosphorus metabolism in a case of nontropical sprue with associated tetany are reported.

2 It is emphasized that the low serum calcium and phosphorus, the osteoporosis and the tetany seen in cases of sprue are not the result of parathyroid deficiency, but are due to the inadequate absorption of

31 Sokhey, S. S., and Malandkar, M. A. Pancreatic Function in Sprue, *Indian J. M. Research*, **25** 921 (April) 1928. (See this article for additional references.)

32 Irving, L., and Ferguson, J. The Influence of Acidity in the Intestine Upon the Absorption of Calcium Salts by the Blood, *Proc. Soc. Exptl. Biol. & Med.* **22** 527 (May) 1925. Babbott, F. L., Jr., Johnston, J. A., and Haskins, C. H. Gastric Acidity in Infantile Tetany, *Am. J. Dis. Child.* **26** 486 (Nov) 1923.

33 Porter, W. B., and Rucker, J. E. The Treatment of Non-Tropical Sprue with Liver Extract, *Am. J. M. Sc.* **179** 310 (March) 1930. Elders, C. Behandlung der Tropischen Sprue, *Med. Welt* **3** 167, 1929.

calcium and phosphorus from the gastro-intestinal tract because of the existing diarrhea

3 In the case reported, improvement took place coincident with the giving of 6 vials of liver extract daily. Subsequently, 2 vials a day were found to be sufficient.

4 A very low value for serum total base (124 mg per hundred cubic centimeters) is reported.

Book Reviews

THE RENAL LESION IN BRIGHT'S DISEASE By THOMAS ADDIS and JEAN OLIVER
Price, \$16 Pp 650, with 160 full page illustrations and 21 text illustrations
New York Paul B Hoeber, Inc, 1931

In this modern day of haste, with its attending evil, superficiality, the survey of a book such as that of Addis and Oliver affords unusual pleasure. Unusual not only because of its thoroughness, a thoroughness that carries the conviction of authority, but because the presentation is as forceful as it is personal, and the subject matter so logically and clearly studied and developed, that there is never any doubt in the mind of the reader that the objectives of the authors have been unquestionably achieved. To call it a landmark were trite. To say that it reflects genuine credit on American medicine is but fair appreciation of the enormous labor, the careful observation and the keen analysis that have been condensed in the volume.

It differs from many other works dealing with the subject because of its absolute objectivity. It is built on bed rock. And even to those who may stray from the narrow pathway of the microscope into the wider, though less certain, thoroughfares of pathologic physiology, the very solid pathologic basis is as refreshing as it is convincing. So, too, the clinical observations are based not only on thorough study, but on urinalyses that are unique in their approach to quantitative exactitude—methods that have been under development by Addis for many years. The reviewer would like, in passing, to emphasize their value, as they are not sufficiently known to the medical profession at large. Addis has not only worked out the quantitative analysis of the urinary sediment and reasonably satisfactory measures of the maximum functional capacity of the renal tissue, in themselves of enormous clinical value, but has made such functional determinations over long periods of time. Only by such long-continued functional surveys can a true picture of the clinical condition be obtained. His insistence that the clinician himself should examine the sediment strikes a responsive cord. Too much routine work is delegated to technicians. Chemical determinations are justifiable, examination of the urinary sediment, with care for its proper collection, should be done by the physician himself. The authors make it very evident that the urine so examined offers a store of information about the patient to the careful examiner. Were there nothing else of value, the first four chapters (I Introduction, II Clinical Methods, III Clinical Definitions, IV A Clinical Classification of Bright's Disease in Accordance with the Nature of the Renal Lesion) would in themselves justify the book.

Oliver made a pathologic study of the seventy-two cases of Bright's disease that form the basis of the work. Each case is discussed in detail: the history, the clinical picture, the salient gross pathologic changes and the description of the microscopic examination. The 160 plates (magnified 20 and 120 times) represent photomicrographs that are in themselves instructive as well as technically excellent. The reviewer has been particularly impressed with the descriptive terseness, all nonessential detail having been omitted, which in itself is convincing evidence of the sense of proportion that is conveyed by the entire book.

To illustrate finer details that are essential in the analysis presented in the final chapters (VI Pathological Definitions, VII The Clinical and Pathological Observations, VIII Clinical Summary and Comparison of Clinical and Pathological Data, IX A Correlation of the Clinical and Pathological Observations, X A Theoretical Description of the Course and Sequence of the Pathological Processes in Bright's Disease, XI A Classification and Theory of Bright's Disease), Femberg has made a series of drawings of high power fields. Their quality is in keeping with the rest of the book in which typography, binding, form and paper are of exceptionally high standard.

The reviewer has called attention to the mature balance that pervades the book, and to its objectivity. It has not been the purpose of the authors to spread—limitation has permitted depth. There has been no attempt, for instance, to discuss hemorrhagic Bright's disease from the point of view of general capillary damage. The focus is on the kidney, and is clearly so stated in the title. This limitation in no wise lessens the value of the book to the clinician or to the scientific investigator.

Addis and Oliver have contributed a book that should be of enormous value to every clinician, stimulating, intensely practical and thoroughly readable and understandable as books are apt to be when the authors are masters of their subject.

NOGUCHI. By GUSTAV ECKSTEIN. Price, \$5. Pp 419. New York: Harper & Brothers, 1931.

Three years after Hideyo Noguchi, a famous Japanese bacteriologist, lost his life in Africa through his untiring search for the organism responsible for yellow fever, the general reading public is made acquainted with the facts of his life through this biography by Gustav Eckstein. This volume ought to prove interesting to the members of the medical profession whether they knew Noguchi personally or are familiar with his work. However, the lack of technical language and the lucid explanations of all experimental procedures indicate that the author intended to bring the book to the attention of the layman as well as to that of the physician.

If one can overlook marked deficiencies in the literary style and an all too frequent repetition of irrelevant detail, one will be able to gain a good deal of pleasure from this account of Noguchi's colorful career and his valuable contributions to the study of organisms responsible for disease. The numerous facts that the author brings to bear on each period of Noguchi's life, from his very humble boyhood to his sad death, indicate that he had access to a vast number of letters written by, to and about Noguchi, as well as an insight into the circumstances of his life. One feels that if the author had exercised greater discrimination in his choice of material, he could have written a much finer book. He presents so many facts that he is unable to give proper emphasis to the really important things.

However, whatever faults may be noted in regard to technical qualities, it is apparent that Mr. Eckstein has painted a convincing word portrait of a remarkable personality. Noguchi's accomplishments are secondary to his character, and whenever a description of a unit of his work occurs, it serves to illustrate some trait or traits in his character. Although the work that he executed marked him as a "genius" he is, nevertheless, as one examines his reflection in this book essentially a "man"—happy and proud when he succeeded in something he set out to do, discouraged and despondent when he failed, sensitive to criticism, and appreciative of courtesies shown him.

In order that the reader may understand something of the interest that lies in this book, certain traits of personality will be illustrated by quotations from it. Time after time the author describes the intensity with which Noguchi applied himself to his work. "He was in the laboratory through the whole of last night, through the whole of yesterday, through the whole of the night before." One marvels at the manner in which his will was able to dominate bodily weaknesses. That he was able to live to the age of 51, in spite of his devotion to labor and a body weakened by disease, is nothing short of miraculous. Rather humorous are the anecdotes dealing with his lack of understanding of business matters and the resultant lack of funds. "As to science I am a great success but as to financial conditions I am below zero point." There is something pathetic in his effort to hide the deformed left hand which had been so severely burned when he was a boy. "He has learned to hide his hand." He drops his cap over it, or folds his arms in front of him slipping the left hand under the elbow. When triumph comes to him, he says, "I am the first to cultivate the sprockete of

syphilis In Copenhagen they gave me the Royal Medal It is said that the Swedish crown intends to decorate me I have sat with great men of science and become intimate with them" His elation at success is no more marked than his despondency at failure "I feel only the smallness and weakness of man" His understanding of genius corresponds with that of some psychologists "There is no such thing as genius It is hard work That is genius"

These are but a few angles of the character which Mr Eckstein stresses. Noguchi's name has gone down in medical history because of his work and the methods he employed, and now the facts of the life that lay back of these accomplishments will go on record and thus be saved from oblivion. Those of the medical profession who value personal qualities in their colleagues and predecessors cannot help but be inspired by the life story of this great little Nipponese who, through his work in America, received the recognition of the highest scientific orders throughout the world.

THE PHYSICIAN OF THE DANCE OF DEATH By ALDRED SCOTT WARTHIN
Price, \$7.50 Pp 142, with 92 illustrations New York Paul B Hoeber, Inc., 1931

The Dance of Death in art and literature is an expression of the common conception of death as a leveler and conqueror of all. The conception is doubtless as old as the time that man first began to philosophize about his existence and his end, but its expression in art began in the Middle Ages, and was most frequent in that morbid period. As Warthin says, "The most satisfactory explanation of the origin of the Toten Tanz motive is to be found in the psychology of the times, which constantly stressed the thought of death and the vanity of all earthly things." "It was a neurotic and psychopathic age, as shown in its superstitions, its religious fanaticism, its sensuality, belief in witchcraft and magic." But the idea has never since failed to interest artists when in their contemplative moods, and it is still used by them even down to pictures of the last Great War. Of course expression of the idea varies with the varying mental attitude of succeeding centuries, but the essential theme is the same.

The study of the subject became a hobby of Warthin's in his professional youth. "In 1893, a young medical student on his way to Vienna passed through Nuremberg. In a shop window, in the street leading up to the castle, a print caught his eye. It was Albrecht Durer's 'Ritter, Tod und Teufel'. So deep was the impression made by it upon the susceptible, perhaps somewhat sentimental, youth, that the print at once became his own, and the brave Knight, who feared neither Death nor Devil, came to represent to him an ideal of life." The ideal became in Warthin a fine one, to fear neither death nor devil and to love truth.

From that time Warthin began to collect illustrations of the Dance of Death, and this volume is a result of that hobby. A great number of illustrations are reproduced, nearly all from copies or originals in his collection. The volume ends with a bibliography of the Dance of Death in Dr Warthin's collection, and in addition a bibliography of the short list not in his collection. It makes a fascinating book, both in text and in illustrations. One can spend, not an interesting hour, but interesting hours analyzing the various ways the theme is illustrated in the many cartoons. Warthin has made this exercise easier by his text.

This diversion was one out of which he evidently got much interest. As he says, "He can wish his colleagues no greater pleasure than the pursuit of such a hobby." It is a fine illustration of the pleasure of a hobby, something the reviewer agrees with Warthin that every man should develop early in his career for his own satisfaction. One will be better for it, if it is a hobby of cultural interest, as it was with Warthin, and if it is a hobby that involves some aspect of one's own philosophy of life. The latter was evidently true in Warthin's case. His vocation emphasized death as an item of his philosophy, and this hobby, perhaps, was a result. But it was not a neurotic or a morbid interest, it was a frank

acceptance of death as a normal physiologic end, and Warthin's was the sane attitude of quiet courage of the well known lines of Shakespeare with which Warthin ends his book

"It seems most strange that men should fear,
Seeing that Death, a necessary end,
Will come when it will come"

This handsome book has two good reasons for being on the shelves of physicians (1) the interest of the book itself and (2) as a reminder of a successful diversion for a physician of culture

The publisher deserves a word of praise, the book is a fine example of the printer's art

RADIUMTHERAPIE, METHODEN UND AUSSICHTEN By DR F GUDZENT, a o Professor an der Universität Berlin Band V Medizinische Praxis, Herausgegeben von Grote, Fromme, Warnekros Paper Price, 6 50 marks Pp 116, with 53 illustrations Leipzig Theodor Steinkopff, 1929

The booklet serves as a short, concise handbook of reference regarding the indications and usage of radium in medicine A short resume of the discovery of radium and of its physical and chemical properties is given The decay of radium and its emanation are explained, and filtration principles with various types of radium applicators are illustrated and explained

The biologic response of skin, muscle, tendon, cartilage, bone, nervous tissue and the blood to the action of the rays from radium is reported

Indications and technic of treatment in gout, rheumatism, neuritis, blood dyscrasias and chronic suppuration by inhalations of emanation and by drinking and bathing in radio-active waters are given, and the radium content of the waters of various popular German watering places is included

Types of lesions of the skin amenable to the action of radium are briefly discussed, for deeper tumors, the importance of combined surgery and radium usage is stressed The gynecologic uses of radium are fully entered into

THERAPIE DER ERKRANKUNGEN DES VEGETATIVEN NERVENSYSTEMS Price, 7 marks P 96 Dresden Theodor Steinkopff German Society for the Advancement of Medicine, 1930

This book contains a series of lectures given at Bad Oeynhausen by various specialists The vegetative nervous system is discussed from various points of view in an extremely elementary manner, so that not even a complete survey of the subject may be obtained

The contents are of little interest to the neurologist and cannot be considered worth very much to the internist

THE TREATMENT FOR SECONDARY ANEMIA

A STUDY OF THE RESULTS IN ONE HUNDRED AND TWENTY-SIX
CASES *

CHESTER S. KEEFER, M.D.

BOSTON

AND

CHI-SHIH YANG, M.D.

PEIPING, CHINA

Classification of the Anemias

Methods of Study

Special Clinical Features

Changes in the Tongue

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Rarity of Pernicious Anemia

Various Groups of Anemia

Posthemorrhagic Anemia

Anemias Associated with Undernutrition

Anemias Associated with Chronic Dysentery

Anemia Associated with Kala-Azar

Anemias of Pregnancy

Anemia Associated with Infestation Due to Hookworm

Anemia Associated with Miscellaneous Conditions

Malaria

Chlorosis

Splenic Anemia

Tuberculosis of the Intestines

Results of Treatment

The Value of Liver

The Value of Iron

The Value of Liver Ash

The Value of Liver and Iron

The Value of Liver Extract and Iron

The Response of the Reticulocytes

Summary and Conclusions

For the past two years, we have been engaged in a study of the various forms of anemia that were observed in patients admitted to

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* From the Department of Medicine, Peiping Union Medical College

the general medical wards of the Peiping Union Medical College. The purpose of these observations was to study the course of the blood following various forms of treatment and to obtain information regarding the factors that influence the regeneration of hemoglobin in man. We were aware of the difficulties in drawing conclusions following various forms of treatment because of the many variable factors present in different patients, and it also was evident that many of the factors could not be evaluated quantitatively. In any study of the cause of anemia one usually considers such conditions as loss of blood, the previous diet of the patient, the presence of infection, the reserve supply of materials necessary for the formation of hemoglobin, the function of the bone marrow, the evidences of increased destruction of blood and the total volume of the blood. In many instances it is difficult and sometimes impossible to evaluate the relative importance of each

TABLE 1—*Forms of Anemia Studied*

Type		Number of Cases	
Posthemorrhagic anemia		15	
Dysentery		20	
Malnutrition		17	
Pregnancy		9	
Hookworm		7	
Kala azar		28	
Miscellaneous cases		30	
Malaria	3	Pernicious anemia	2
Chlorosis	4	Syphilis	3
Splenic anemia	4	Typhoid fever	1
Anemia following splenectomy	2	Cirrhosis of liver	1
Chronic nephritis	1	Acute leukemia	1
Tuberculosis of intestines	4	Purpura hemorrhagica	1
Aplastic anemia	2	Cancer of stomach	1
Total number of cases		126	

factor. However, by studying each patient before and after treatment and comparing the results under similar conditions, valuable information may be obtained. In this paper we present the results of a study of 126 patients with anemia.

CLASSIFICATION OF THE ANEMIAS

We did not classify our cases on a basis of the morphologic characteristics of the blood, nor according to the more general classifications such as anemias due to increased destruction or defective formation of the blood, but we divided them into groups according to the condition with which the anemia was associated, and the various factors contributing to the production of the anemia were analyzed. Thus, the anemia associated with chronic dysentery was studied from the point of view of loss of blood, the previous diet of the patient, the presence of infection, changes in gastric secretion and the nutritional disturbances caused by the diarrhea. In this way, the various factors precipitating the development of anemia were evaluated. The various forms of anemia studied are summarized in table 1.

METHODS OF STUDY

All of the patients were studied while resident in the hospital and were observed for periods of time varying between twenty-one and one hundred and twenty days. They were examined carefully for evidence of loss of blood, and all of the clinical features were noted. The red blood cells were counted with standardized counting chambers and pipets, and the hemoglobin content was determined by the Sahli method in which a colored glass was used for the standard. This instrument was calibrated with the oxygen capacity method so that 100 per cent was equal to 17 Gm. of hemoglobin or an oxygen capacity of 22.5 per cent by volume. The reticulocytes were counted, the dry smear technic being used. All of these determinations were made in the different patients at intervals varying from one to four days. The morphologic characteristics of the blood were studied, and the presence of nucleated erythrocytes and the changes in the size and shape of the cells were noted. In a number of the cases the exact size of the erythrocytes was measured with a calibrated ocular micrometer, and the Price-Jones curves were plotted.

In evaluating the results of treatment, the rate of the formation of hemoglobin was determined before and after treatment, and the reticulocytes were followed daily. In this way it was possible to reach a conclusion regarding the value of the treatment employed.

SPECIAL CLINICAL FEATURES

Before summarizing the results of the study of the blood, we wish to call attention to a number of the interesting clinical features that were observed. We refer to changes in the tongue, skin, ocular fundi, nervous system and gastric acidity, together with other complicating conditions, such as the various deficiency disorders due to avitaminosis and other nutritional defects.

Changes in the Tongue—Atrophy of the papillae of the tongue was observed in nine patients. The degree of atrophy varied from a disappearance of the papillae in the central portion of the tongue to complete atrophy of all of the papillae. Following recovery from the anemia, the papillae returned and the tongue appeared normal. The natural history of this phenomenon is unknown since it was asymptomatic in all but one patient. In this man, the atrophy had been preceded by recurrent attacks of glossitis. The picture presented by the tongue was indistinguishable from that frequently seen in pernicious anemia. Besides these cases, we have observed atrophy of the papillae of the tongue in three other patients who had chronic dysentery without anemia.

Aside from the conditions mentioned, atrophy of the papillae of the tongue may be observed in sprue, pellagra, dysphagia associated with

anemia, and following gastrectomy, and also in some patients with anemia associated with a chronic infestation due to hookworm. While its exact significance is difficult to appreciate, these changes are usually present in patients who are undernourished or who have a pathologic process that interferes with nutrition. It may be added that these conditions may be present without gastric anacidity.

Changes in the Skin—The lesions of the skin that are characteristic of pellagra were present in two patients and hyperkeratosis folliculosis in three. The latter condition was extensive, and presented an extraordinary clinical picture. Frazier and Hu¹ made a special study of this condition and attributed these changes to deficiency in vitamin A, they reported the results of their investigations in detail elsewhere. All of these lesions disappeared following the recovery from anemia and establishment of an adequate diet.

Retinal Hemorrhages—Hemorrhages into the retina are observed commonly in patients with pernicious anemia, in the anemias associated with hemorrhagic phenomena and in chronic nephritis, but they are uncommon in other forms of anemia. In the cases that we studied, numerous hemorrhages were present in the retinas of four patients. In three, the anemia was associated with chronic dysentery, and in one, it resulted from bleeding hemorrhoids. In all, the erythrocyte count was less than 1,500,000 cells. The hemorrhages were associated with patches of exudation which resembled those seen in patients with retinal vascular changes. It seemed to us that the appearance of hemorrhage in the eyegrounds depended on the severity of the anemia rather than its cause. Heine² called attention to the hemorrhages occurring in the ocular fundi in the various anemias in man, and stated that this condition is more common in pernicious anemia than in other forms of anemia.

Changes in the Nervous System Associated with Anemia—Changes in the nervous system were present in seven patients. In five, the clinical observations were characteristic of subacute combined degeneration. In two of these, typical pernicious anemia was present. Of the other three cases, two were associated with chronic dysentery, and the third was present in a woman with gastric anacidity and anemia resulting from loss of blood. Gastric anacidity was present in all of the five patients, but in one patient in whom the signs were associated with anemia and chronic dysentery, the gastric anacidity was only temporary.

1 Frazier, C. N., and Hu, C. H. Hyperkeratosis Follicularis. Preliminary Report, Tr. International Dermatological Conference, Stockholm, 1930.

2 Heine, L. Die Krankheiten des Auges, Berlin, Julius Springer, 1921, p. 392.

Peripheral neuritis was observed twice. In both cases, it was associated with anemia and chronic dysentery, but it was unassociated with gastric anacidity.

It was striking that these maladies were present in patients who had nutritional defects, and the isolated observation of the presence of subacute combined sclerosis in a patient with anemia and a temporary derangement of gastric function is of interest in view of the relationship existing between gastric anacidity, subacute combined sclerosis and nutritional defects.

The development of peripheral neuritis in association with chronic dysentery and anemia was of interest from the standpoint of etiologic diagnosis. The questions naturally arose: Was the peripheral neuritis due to deficiency in vitamins, so-called beriberi, or was it the result of the dysenteric infection? At present we do not know of any method of answering these questions conclusively. In the future, similar cases should be studied from the point of view of a deficiency disorder being the cause of neuritis.

Changes in Gastric Secretion—It is becoming clearer that alterations in gastric secretory function are of considerable importance in predisposing many patients to the development of pernicious anemia. This belief is due to the recent important work of Castle and his associates, Townsend and Heath.³ They have been able to demonstrate conclusively that in patients with gastric anacidity and pernicious anemia, the stomach is incapable of secreting a substance (an intrinsic factor, possibly an enzyme) that is present in normal human gastric juice and is capable of interaction with protein or closely related substances, resulting in the production of material having a marked hematopoietic effect when administered to patients with pernicious anemia. Moreover, Castle and his co-workers have shown that some patients with achlorhydria and anemia may be able to secrete this substance, whereas in these patients the stomachs do not secrete hydrochloric acid, and they have also observed patients with an anemia closely simulating the blood picture of pernicious anemia, who were capable of secreting hydrochloric acid, but in whom the gastric juice was ineffective when tested for its ability

3 Castle, W. B. Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia. I. The Effect of the Administration to Patients with Pernicious Anemia of the Contents of the Normal Human Stomach Recovered After the Ingestion of Beef Muscle, *Am J M Sc* **178** 748, 1929. Castle, W. B., and Townsend, W. C. II. The Effect of the Administration to Patients with Pernicious Anemia of Beef Muscle After Incubation with Normal Human Gastric Juice, *ibid*, p. 764. Castle, W. B., Townsend, W. C., and Heath, C. W. III. The Nature of the Reaction Between Normal Human Gastric Juice and Beef Muscle Leading to Clinical Improvement and Increased Blood Formation Similar to the Effect of Liver Feeding, *ibid* **180** 305, 1930.

to produce the effective principle from beef muscle. These observations not only explain why anemia does not develop in some patients with gastric anacidity but they may also explain why pernicious anemia does not develop in many patients with anacidity, and why it develops in some patients with normal gastric acidity.

It is clear, then, that alterations in gastric secretory function are of importance in the study of any form of anemia. When the gastric secretory function of patients with anemia is studied repeatedly, histamine being used as a test stimulus, two types of response are observed: a permanent type of gastric anacidity, or a temporary suppression of "free" acid. In the group under discussion, the gastric secretion of sixty-five patients was studied and gastric anacidity was found in sixteen. In six, it was only temporarily present, in two, there was typical pernicious anemia, and of the remaining eight, only three were examined more than once. We were unable to establish any definite correlation between gastric anacidity and anemia in most of our patients. However, a final answer to the question of the relationship between various forms of anemia other than pernicious anemia and alterations in gastric function cannot be given at the present time.

Association with Deficiency Disorders—One of the interesting features in some of the patients observed was the evidence of deficiency disorders, such as keratomalacia, scurvy, osteomalacia, rickets and "edema disease." We observed keratomalacia in five, edema in ten, rickets in two, scurvy in two and osteomalacia in one. In a previous paper, we⁵ pointed out that deficiency disorders such as keratomalacia, beriberi, rickets, scurvy, osteomalacia and tetany may be present without anemia, and if anemia is present in such patients it was concluded that it was due to a deficiency of substances other than vitamins A, B, C and D, or to some complicating factor such as infection. These conclusions were based on a study of the blood in twenty-two cases of keratomalacia, forty-one cases of beriberi, four cases of scurvy, seventeen cases of rickets, thirteen cases of osteomalacia and twenty-two cases of tetany resulting from pregnancy, lactation or a deficient diet. Anemia associated with edema will be discussed under the anemias associated with undernutrition.

Rarity of Pernicious Anemia—During this study we observed only a single typical case of pernicious anemia in a Chinese patient. It has been the experience of all clinicians who have had an opportunity of

4 Chang, H. C., Yang, C. S., and Keefer, C. S. Improvement in Gastric Function in Patients Following Recovery from Secondary Anemia, *Nat. M. J., China* **15** 752, 1929.

5 Keefer, C. S., and Yang, C. S. The Rôle of the Various Vitamins in the Production of Anemia, *Nat. M. J., China* **15** 419, 1929.

studying anemia in Chinese patients to note the infrequency of pernicious anemia. In the clinical records of the first 25,000 patients admitted to the Peiping Union Medical Hospital there were notes of only four cases in which a diagnosis of pernicious anemia seemed justified, and all but one of these were observed before treatment with liver was known. Fu and Sturton,⁶ Morris⁷ and Struthers⁸ observed some cases, but details are lacking. Dr. George R. Minot informed us that he observed two typical cases in Chinese patients in America. The reason for the uncommon occurrence of the disease is not clear. There are two suggestive points. In a study of the gastric contents of patients in whom histamine was used as a test stimulus, Chang⁹ showed that gastric anacidity was present in only 7.5 per cent of the cases studied.

TABLE 2—Results of Treatment for Posthemorrhagic Anemia

Case	Red Blood Cells, Millions		Hemoglobin, per Cent		Reticuloocytes, per Cent		Types of Treatment
	Before Treat- ment	After Treat- ment	Before Treat- ment	After Treat- ment	Before Treat- ment	After Treat- ment	
1	3.0	5.0	45	85	0	3.5	Transfusion
2	4.25	5.0	50	85	0	7.0	Transfusion
3	3.5	3.75	50	75	0	8.0	Transfusion
4	1.25	3.75	20	65	0	2.0	Transfusion
5	2.5	4.0	30	55	0	1.0	Iron
6	4.7	5.7	52	75	0	7.5	Iron
7	2.25	4.75	35	90			Liver and iron
8	3.0	5.0	35	85	0	1.5	Liver and iron
9	4.9	5.18	50	80	0.4	6.6	Liver and iron
10	3.05	4.0	42	72	0.2	4.8	Liver and iron
11	1.02	4.35	13	80	15.0	8.0	Liver, iron
12	3.46	5.89	43	102	0.8	5.0	Liver, iron and liver
13	1.42	4.34	22	70	1.8	12.0	Liver and iron
14	2.65	3.83	31	49	1.4	1.2	Liver extract
15	1.75	2.35	33	38	3.6	2.4	Liver extract

While it is difficult to compare these results with those obtained from a similar group in the United States, owing to the method employed, it is suggested that the incidence of gastric anacidity in a miscellaneous group of hospitalized patients may be lower in China than elsewhere. Moreover, the difference in the dietary habits of oriental and occidental people may be of importance in explaining the infrequency of pernicious anemia in China. Both of these questions require further investigation.

VARIOUS GROUPS OF ANEMIA

Posthemorrhagic Anemia—We have studied fifteen patients with posthemorrhagic anemia, and the results of treatment are summarized in table 2. The most conspicuous results were obtained following the

⁶ Fu, W., and Sturton, S. D. A Severe Case of Pernicious Anemia, China M. J. **40** 1016, 1926.

⁷ Morris, H. H. Anemias in China, China M. J. **43** 768, 1929.

⁸ Struthers, G., in discussion on Morris (footnote 7).

⁹ Chang, H. C. Personal communication to the authors.

administration of liver and iron Chart 1 illustrates such a case Similar observations have been recorded by Minot, Murphy and Stetson,¹⁰ Murphy and Powers,¹¹ Dyke,¹² Vaughan,¹³ Wahlberg,¹⁴ and others

In drawing conclusions from the results of the treatment of patients with this form of anemia, there are difficulties due to the varying response observed following treatment For example, it is generally

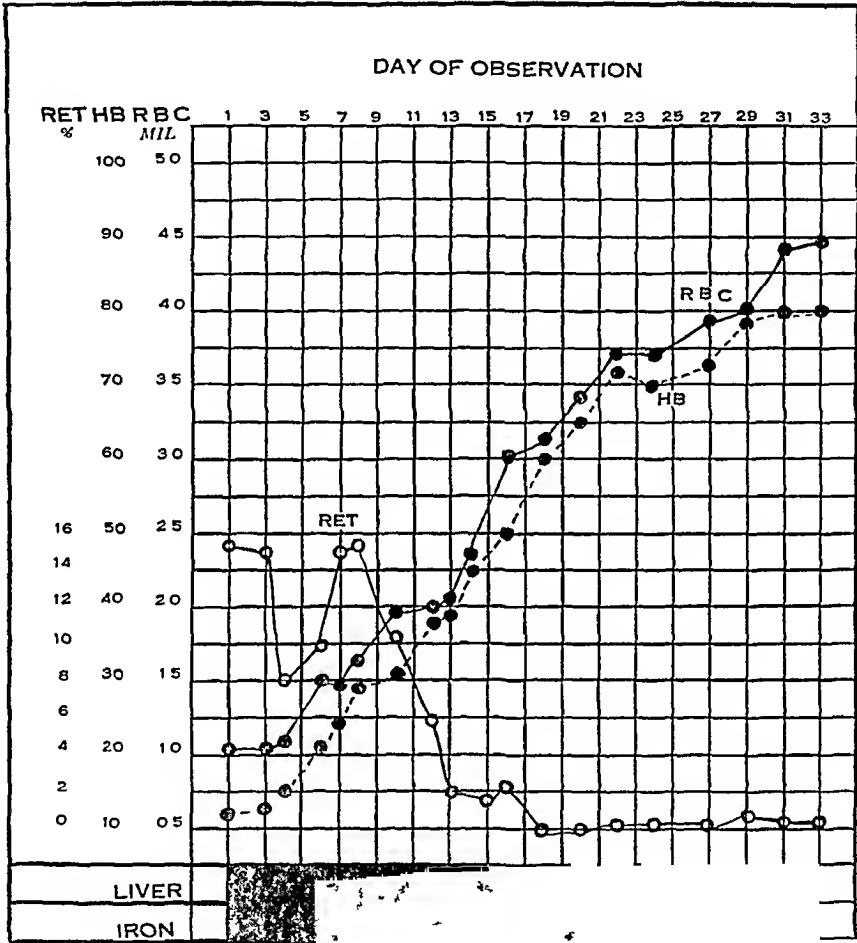


Chart 1—Chart of patient with anemia resulting from chronic loss of blood Recovery was rapid after treatment with liver and iron The reticulocytes were increased before treatment was started

10 Minot, G R , Murphy, W P , and Stetson, R P The Response of the Reticulocytes to Liver Therapy in Pernicious Anemia, Am J M Sc **175** 581, 1928

11 Murphy, W P , and Powers, J H The Value of Liver in the Treatment of Anemia Due to Hemorrhage, Surg, Gynec & Obst **48** 480, 1929

12 Dyke, S C Liver Therapy in Secondary Anemia, Lancet **1** 1192, 1929

13 Vaughan, Janet Critical Review The Liver Treatment of Anemias, Quart J Med **23** 213, 1930

14 Wahlberg, J Liver Diet and Reticulocyte Reaction in Simple Anemia, Acta med Scandinav **72** 143, 1929

believed that the period of recovery following an acute hemorrhage is relatively rapid, that is to say, complete recovery may occur within several weeks after the hemorrhage regardless of treatment. This has been shown to be true in the experimental posthemorrhagic anemias in animals and in similar anemias in man. This rapid recovery is due to the presence of a large amount of reserve material which is available for the regeneration of the red cells, and the hemoglobin. There are patients, however, who continue to have anemia for many weeks following an acute hemorrhage, and recovery may be slow. Such cases have been reported by Dyke,¹² and we have observed similar cases. In these patients the reserve supply of hemoglobin and red cell substances must be small. This view gains support in the experimental work of McCay,¹⁵ who was able to show that animals recovering from a posthemorrhagic anemia might be rendered anemic by a relatively small bleeding, whereas the loss of a similar amount of blood from an animal which had not been anemic previously was not followed by anemia. These observations emphasize the importance of an adequate reserve supply of the substances that build hemoglobin in determining the appearance of anemia and the rate of recovery following acute hemorrhage.

On the other hand, the chronic posthemorrhagic anemias usually present an entirely different problem. In such cases, the reserves have usually been exhausted, and if the materials necessary for regeneration of the blood are not supplied in large quantities in the diet, the rate of recovery will be slow. Whipple and Robschiet-Robbins were the first to emphasize the importance of dietetic therapy in the treatment for this form of anemia. When their dogs had chronic anemia from repeated bleeding, the hemoglobin content of the blood could be maintained at a surprisingly low level for several years, providing the diet was not made up of large amounts of food containing the materials necessary for the regeneration of hemoglobin. They found that liver and kidney contained the largest amount of these substances, but iron and the salts of other metals were also potent. They pointed out that liver and iron produced an effect of the two expected reactions. It is not surprising, therefore, that a similar response may be observed in those anemias in man that are caused by bleeding. It should be emphasized that complete recovery may not occur in less than from four to six weeks in these patients, even following the administration of liver and iron, but this result is as satisfactory as that observed in some patients with pernicious anemia following the use of liver extract, and

¹⁵ McCay, C. M. The Influence of Protein, Blood, Liver, Fat, Iron, and Potassium in the Diet upon the Rate of Blood Regeneration After Hemorrhage in the Rat and Dog, *Am J Physiol* **84** 16, 1928.

recovery is usually considerably more rapid than that observed when these patients recover without such treatment

It is manifest, therefore, that recovery from posthemorrhagic anemia may be accelerated by the use of liver and iron, provided such inhibitory factors as sepsis and continual loss of blood are not present

Anemias Associated with Undernutrition—In a previous paper we¹⁶ reported cases of anemia resulting from malnutrition. The anemia was caused either by faulty diets, or by pathologic processes interfering with normal nutrition, such as chronic diarrhea. Since that time,

TABLE 3—*Anemia of Malnutrition*

Case	Red Blood Cells, Millions		Hemoglobin, per Cent		Reticuloocytes, per Cent		Type of Treatment	Comment
	Before Treat- ment	After Treat- ment	Before Treat- ment	After Treat- ment	Before Treat- ment	After Treat- ment		
36	2.68	4.34	44	80	0.8	6.3	Diet	Typhus
37	3.08	3.99	56	82	3.0	7.0	Diet	Edema
38	3.25	5.0	60	85		2.0	Diet	Osteomalacia
39	2.5	4.75	45	85		3.0	Diet	Scurvy
40	3.40	4.70	53	87	0.8	13.2	Diet	Edema
41	3.16	4.02	59	80	5.6	4.6	Diet	Edema
42	3.00	5.41	33	97	0.6	4.4	Iron	
43	38.9	4.02	44	75	0.6	9.0	Iron	Edema
44	3.00	4.95	53	89	3.2	5.0	Iron	Edema
45	2.84	3.81	43	63	0.2	9.8	Liver and iron	Keratomalacia
46	2.84	4.49	39	83	0.2	10.0	Liver and iron	
47	1.47	3.81	18	73	7.0	17.4	Liver and iron	Keratomalacia
48	1.84	4.36	26	85	0.0	13.0	Liver and iron	
49	0.69	5.25	17	90	0.2	35.8	Liver ex- tract	In childhood
50	3.00	5.25	52	85	6.0	0.0	Liver ex- tract	In childhood
51	3.23	2.46	54	42	0.0	5.2	Diet, liver and iron	Gangrene of lung, death
52	1.8	2.5	34	42	5.8	13.6	Diet, liver ex- tract and iron	Typhus, death

other similar cases have been studied. The anemias resulting from faulty diets are summarized in table 3. In this group, the evidence that supported the conclusion that the anemia resulted from malnutrition was the history of inadequate diets, the presence of undernutrition, the association of nutritional defects such as avitaminosis and edema, and the recovery from the anemia following adequate diets supplemented with substances that tend to build hemoglobin, such as liver and iron.

The importance of faulty diets as a cause of obscure anemias is becoming greater as the various forms are studied. By recognizing this fact and studying these cases, information regarding the exact nature of the substances that are lacking and the deficiency of which is responsible for the development of the anemia may be obtained. In studying

¹⁶ Keefer, C. S., and Yang, C. S. Anemia of Undernutrition. Report of Cases with Results of Treatment, Nat. M. J., China 15:701, 1929.

the blood of a number of patients with deficiencies due to a lack of vitamins A, B, C and D, we concluded that all of these avitaminoses could exist in man without anemia, although anemia was present in some instances. In the cases in which anemia was present, we concluded it was probably the result of deficiencies in other food substances or of infection. Recently, Mettier, Minot and Townsend¹⁷ reported eight cases of scurvy in which there was a concomitant anemia. They showed that when the patients were given food containing a large amount of vitamin C there was definite improvement in the blood picture with an increase in the reticulocytes. They concluded that the anemia in these patients was due to a lack of vitamin C, but that it was influenced by other factors such as infection, arteriosclerosis or hemorrhage.

TABLE 4—*Erythrocytes and Hemoglobin in Patients with Edema Resulting from Malnutrition*

Case	Red Blood Cells, Millions	Hemoglobin (Sahli), per Cent	Comment
1	4.8	95	Dysentery, dehydration
2	4.6	95	
3	7.2	134	
4	4.9	85	
5	4.2	84	
6	4.4	78	
7	3.04	77	
8	3.6	75	
9	3.8	70	
10	3.4	60	
11	3.4	60	
12	4.9	52	Pneumonia, empyema
13	3.0	50	
14	4.6	49	
15	3.5	36	
16	2.1	35	

At the time we recorded the observations on the blood in the various avitaminoses, observations on the blood in so-called edema were not given. Since then, sixteen patients with this disorder have been observed and the blood counts of this group are recorded in table 4. From the table it is evident that this condition may be present without anemia. The hemoglobin content, however, was below 80 per cent in eleven patients and below 70 per cent in seven. In the patients with anemia, recovery followed a balanced diet containing adequate amounts of protein, fat and carbohydrate, or it occurred after the use of iron. During recovery, the reticulocytes usually increased as in the other forms of anemia.

It is apparent, then, that anemia develops in many patients who have been on faulty diets, but it is not clear which elements through their deficiency are responsible for the anemia. In spite of this fact, the

¹⁷ Mettier, S. R., Minot, G. R., and Townsend, W. C. Scurvy in Adults, Especially the Effect of Food Rich in Vitamin C on Blood Formation, J. A. M. A. **95** 1089 (Oct 11) 1930.

regeneration of the hemoglobin may be accelerated in these cases by adequate diets—liver or iron

Chart 2 shows the course of the blood in a patient with anemia due to malnutrition

Anemias Associated with Chronic Dysentery—Anemia associated with chronic dysentery was observed in twenty patients We¹⁸ have described in detail elsewhere the clinical features and the response of

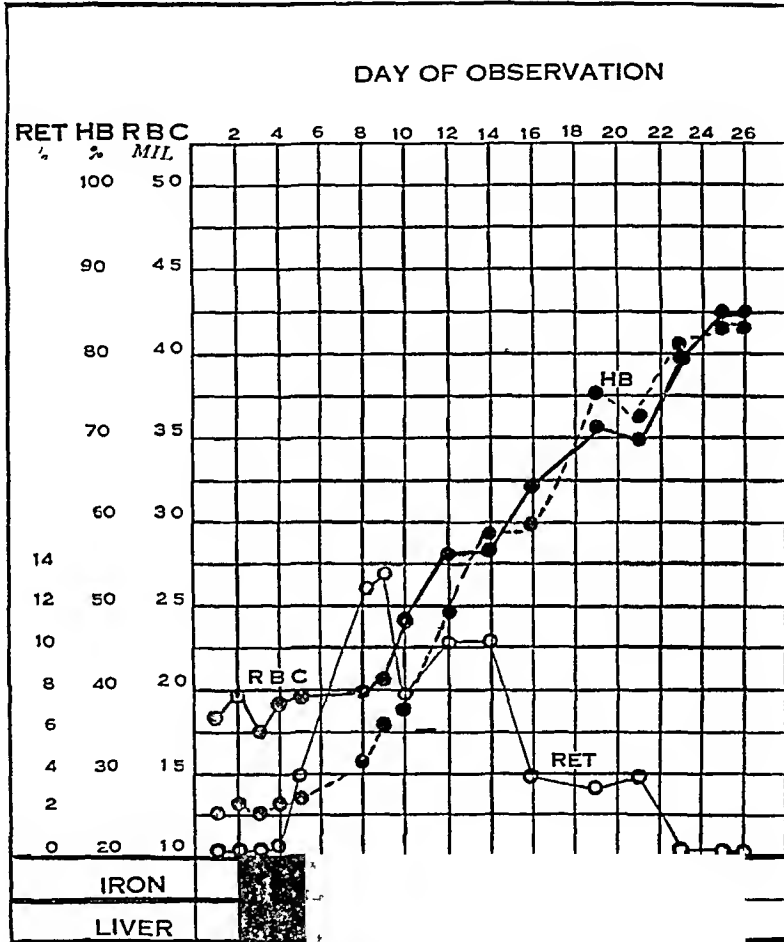


Chart 2—Chart of patient with anemia resulting from partial starvation Recovery was rapid following an adequate diet supplemented with liver and iron

the anemia to treatment in some of these patients To recapitulate Anemia usually developed in these patients only after the dysentery had been present for two months or longer, and then it appeared most fre-

18 Keefer, C S , Huang, K K , and Yang, C S The Importance of Under-nutrition in the Production of Anemia Associated with Chronic Dysentery and Tuberculosis of the Intestine, Nat M J, China 15 743, 1929 Keefer, C S , Yang, C S , and Huang, K K Anemia Associated with Chronic Dysentery Clinical Considerations with Special Reference to the Cause and Treatment, Arch Int Med 47 436 (March) 1931

quently in those who had been on inadequate diets. The loss of blood in the stools and the part played by the infection and by gastric anacidity, when it was present, were only minor contributory factors. As a result of our observations, we concluded that the anemia resulted from the disturbance in nutrition which followed the chronic diarrhea and from the inadequate diet, and that other factors such as loss of blood, gastric anacidity and infection played an insignificant part.

The anemia varied in its morphologic characteristics and in its severity. Both hyperchromic and hypochromic types of anemia were observed, and the red blood cells were, by actual measurement, smaller or larger than normal. During recovery the reticulocytes increased in number, regardless of the form of treatment. The lower the red cell count before recovery, the higher were the reticulocytes at the peak of the rise.

In the group as a whole, we observed all of the clinical features that are said to be characteristic of pernicious anemia, including atrophy of the papillae of the tongue, subacute combined degeneration, gastric anacidity of the temporary and permanent type and an anemia that responded to liver extract.

The response to treatment varied considerably in different patients. In some, excellent responses were observed following the exhibition of liver extract or iron. In others, varying rates of recovery were observed following other forms of treatment such as high caloric diets or the recovery from the dysentery.

The best methods of treatment in this form of anemia were rest in bed, high caloric diet, local treatment of the intestinal lesions and supplementing the diet with liver and iron. In some cases transfusion of blood was helpful. One cannot predict which form of therapy will be effective in an individual case. If liver fails, it is necessary to give iron in order to determine its potency. The results of treatment are summarized in table 5.

From these observations it is clear that the syndrome of pernicious anemia can appear without changes in gastric acidity in patients who have been on inadequate diets and who have a pathologic process interfering with normal nutrition. Furthermore, these observations support the hypothesis that pernicious anemia is a deficiency disease.

Anemia Associated with Kala-Azar—Kala-azar is a parasitic disease, invariably associated with changes in the blood if the infection has been present for any length of time. In studying a number of patients with kala-azar, Keefer, Khaw and Yang¹⁹ pointed out that there was a depression of all the elements in the blood including the erythrocytes, hemoglobin, white cells and platelets. The leukocytes and platelets were

19 Keefer, C S, Khaw, O K, and Yang, C S. The Anemia of Kala-Azar, Nat M J, China **15** 731, 1929.

usually reduced before the hemoglobin and erythrocytes. These changes caused symptoms of anemia, predisposition to infection and thrombocytopenic purpura hemorrhagica. In studying the blood platelets in these patients, Yang and Ch'en²⁰ found that they might be further depressed by treatment with antimony compounds or by some infections.

The cause of the anemia in this disease is not clear, although it is recognized that the characteristic changes in the tissue resulting from the infection are most prominent in the organs that form blood. In many respects these anemias resemble those observed in the so-called myelophthisic anemias, the result of carcinomatoses of the bone marrow.

TABLE 5—Results of Treatment in Cases of Anemia Associated with Chronic Dysentery

Case	Red Blood Cells, Millions		Hemoglobin, per Cent		Reticuloocytes per Cent		Treatment
	Before Treat- ment	After Treat- ment	Before Treat- ment	After Treat- ment	Before Treat- ment	After Treat- ment	
16	2.9	4.3	74	85	4.5		Spontaneous
17	2.2	4.5	60	80	2.0		Spontaneous
18	1.0	3.75	20	75	0.0	1.4	Transfusion
19	3.0	4.5	50	70	0.0	8.0	Transfusion
20	2.25	3.25	45	60	0.0	2.0	Transfusion
21	1.44	5.21	22	88	1.3	28.0	Full diet, cod liver oil
22	1.1	4.17	21	78	1.5	19.0	Full diet, cod liver oil
23	1.61	3.66	19	70	9.0	5.0	Diet, transfusion, iron
24	1.10	4.62	12	90	0.0	26.6	Iron
25	2.8	4.7	51	89	3.0	8.6	Iron
26	3.59	4.36	66	95	1.0	9.0	Iron
27	0.66	4.53	15	96	1.8	38.6	Liver extract
28	2.52	3.97	54	75	0.4	5.0	Liver ash, iron, transfusion
29	3.03	4.89	52	100	0.6	6.0	Liver extract, iron
30	2.0	5.22	35	82	0.8	5.6	Liver extract, liver and iron
31	2.85	3.58	54	85	1.2	7.6	Liver extract, liver and iron
32	4.46	5.0	52	80	0.0	14.4	Liver extract, liver and iron
33	1.80	1.20	34	35	1.4	1.8	Liver extract
34	1.47	2.62	31	56	1.2	5.4	Transfusion, diet
35	3.05	2.80	45	46	1.6	2.8	Iron

osteosclerosis or leukemia. The exact method of inhibition of the formation of blood in these cases, however, remains a mystery.

In treating these patients for anemia, we found that several measures were useful, namely, transfusion of blood, treatment of the infection with antimony compounds, elimination of intercurrent infections and improving the general nutritional state. The results are summarized in table 6.

Anemias of Pregnancy—The so-called anemias of pregnancy are seen most frequently during the latter term of gestation and occur more often in women who have had multiple pregnancies, particularly when the pregnancies have occurred in rapid succession. The anemia may recur in subsequent pregnancies, and many cases show a tendency to spontaneous recovery following childbirth. The severity of the anemia

²⁰ Yang, C. S., and Ch'en, K. T. The Blood Platelets in Kala-Azar, Nat. M. J., China 16:34, 1930.

values and is characterized by a depression of the erythrocytes and the hemoglobin. Pallor and the symptoms of anemia are present, and in some cases, fever, retinal hemorrhages, moderate cardiac enlargement with hemic murmurs, enlargement of the liver and spleen and edema of the lower extremities may be observed. The leukocyte count is usually normal.

The treatment for these anemias has changed during the past few years, since it has been shown that regeneration of the hemoglobin and the red cells can be accelerated by the feeding of liver or liver

TABLE 6—*Anemia Associated with Kala-Azar*

Case	Red Blood Cells, Millions		Hemoglobin, per Cent		Reticuloeytes, per Cent		Type of Treatment
	Before Treat- ment	After Treat- ment	Before Treat- ment	After Treat- ment	Before Treat- ment	After Treat- ment	
69	2.25	3.0	36	45			Urea stibamine
70	2.56	4.0	45	65			Urea stibamine
71	3.00	3.5	55	66			Urea stibamine
72	2.5	4.0	55	85			Urea stibamine
73	3.5	4.0	65	70			Urea stibamine
74	3.25	4.0	60	55			Urea stibamine
75	2.25	3.5	42	70			Urea stibamine
76	2.5	3.0	45	45			Urea stibamine
77	1.5	3.25	25	50			Urea stibamine
78	3.0	4.25	55	89			Urea stibamine
79	3.0	4.0	50	80			Urea stibamine
80	3.5	4.25	65	70			Urea stibamine
81	4.0	4.0	60	60			Urea stibamine
82	4.0	4.70	70	85			Urea stibamine, transfusion
83	1.5	2.5	28	40	2.1	2.1	Urea stibamine, transfusion
84	1.5	1.7	18	45	4.1	3.1	Urea stibamine, transfusion
85	2.0	4.0	40	60	3.1	3.0	Urea stibamine, transfusion
86	3.5	4.5	60	90	2.1	2.0	Urea stibamine, transfusion
87	1.5	2.5	15	30	0.0	1.0	Urea stibamine, transfusion
88	2.5	3.75	40	55	2.0	2.0	Urea stibamine, transfusion
89	1.8	4.25	35	80	2.0	2.0	Urea stibamine, liver and iron
90	2.25	2.25	45	35	2.0	2.4	Urea stibamine, liver and iron
91	3.0	4.5	40	70	2.0	2.0	Urea stibamine, liver and iron
92	2.4	2.0	40	70	2.0	2.0	Urea stibamine, liver and iron
93	2.1	4.0	44	45	0.4	4.6	Urea stibamine, liver and iron
94	2.1	4.0	35	75	2.0	8.0	Urea stibamine, liver and iron
95	2.5	4.0	47	67	2.0	10.0	Urea stibamine, liver and iron
96	3.76	4.0	60	70	1.6	3.2	Urea stibamine, liver and iron

extract, or by combinations of liver and iron or by iron alone. This form of treatment has been reviewed recently by Vaughan,¹³ Strauss²¹ and Yang and Keefer.²² We have had an opportunity of observing nine cases, and in our experience the feeding of liver and iron has been of value. These cases are summarized in table 7. Infection may inhibit the rate of regeneration of the blood, but many immature cells may appear in the peripheral circulation following treatment with liver even under these circumstances. In one such patient whom we observed, the bone marrow showed a marked erythroblastic hyperplasia.

21 Strauss, M. Chlorotic Anemia of Pregnancy. A Report of Three Cases, *Am J M Sc* **180** 818, 1930.

22 Yang, C. S., and Keefer, C. S. The Anemias of Pregnancy, *Nat M J, China* **16** 159, 1930.

The cause of these anemias remains obscure. Certain facts exist, however, which suggest that these anemias develop in the patients who do not receive enough of the essential materials necessary for the regeneration of the hemoglobin during pregnancy, and the increased demands caused by the pregnancy are sufficient to cause the anemia to appear. These cases should be investigated further with these facts in mind.

Anemia Associated with Infestation Due to Hookworm—The cause of the anemia in infestation due to hookworm is unknown. We have studied seven patients with moderately severe anemia and infestation.

TABLE 7—*Anemia Associated with Pregnancy*

Case	Red Blood Cells, Millions		Hemoglobin, per Cent		Reticuloeytes, per Cent		Comment
	Before Treat- ment	After Treat- ment	Before Treat- ment	After Treat- ment	Before Treat- ment	After Treat- ment	
53	1.0	3.75	25	78			Blood transfusions (three)
54	2.0	4.25	20	75	1.0	2.5	Blood transfusions (three)
55	2.5	4.0	45	80	1.0	2.0	Blood transfusions and typhoid
56	4.15	5.0	54	85	2.2	7.0	Iron
57	2.15	3.75	36	75	0.0	11.0	Liver
58	2.97	4.32	53	81	6.8	7.0	Liver and iron
59	3.01	4.83	43	64	2.6	3.6	Liver*
60	2.0	3.0	49	61	0.2	11.0	Iron, liver extract*
61	1.37	2.89	22	47	0.2	13.0	Liver and iron, pyelonephritis, death

* Under hospital observation only two weeks. Blood counts normal six months after discharge.

TABLE 8—*Results of Treatment for Anemia Associated with Infestation Due to Hookworm*

Case	Red Blood Cells, Millions		Hemoglobin, per Cent		Reticuloeytes, per Cent		Type of Treatment	Comment
	Before Treat- ment	After Treat- ment	Before Treat- ment	After Treat- ment	Before Treat- ment	After Treat- ment		
62	3.36	5.11	40	91	1.8	14.0	Liver and iron	123 worms
63	2.38	4.6	30	85	5.0	13.0	Liver and iron	?
64	3.5	4.89	40	86	3.6	10.0	Liver and iron	?
65	2.55	4.43	47	86	4.2	8.0	Liver and iron	10 worms
66	2.94	5.0	32	90	1.4	8.0	Liver and iron	51 worms
67	2.31	4.24	36	100	1.4	9.8	Iron	72 worms
68	2.5	5.0	45	96	1.0	12.0	Iron	146 worms

caused by hookworm and have found that they may recover from the anemia following the administration of liver and iron while they continue to carry the worms. These cases are summarized in table 8.

All of the patients whom we studied had only mild infestations, so that the question may be raised whether the parasitic disease had anything to do with the presence of anemia. At the present time all that can be said is that the patients had anemia associated with infestation due to hookworm and that no other cause was obvious, except that most of the patients had been on faulty diets prior to admission. It will be of considerable interest to determine whether or not the faulty

diets which are consumed by many patients with infestation produced by hookworm are not a predisposing factor in producing anemia and also whether adequate diets may not be capable of accelerating regeneration of the blood before as well as after the expulsion of the worms

It has been pointed out previously that recovery from the anemia may be slow following the expulsion of the worms and that it can be accelerated by giving iron.²³ Day and Ferguson²⁴ never observed complete recovery following this form of treatment until after treatment of the infestation. Whether the complete recoveries that we observed after the administration of liver and iron in infested patients can be obtained in similar patients with a heavy burden of worms remains unsettled. It is clear, however, that recovery from the anemia in this condition can be accelerated by giving an adequate diet supplemented with iron.

Schapiro²⁵ recently called attention to the discrepancy existing between the worm burden and anemia resulting from infestation with hookworms, and expressed the opinion that faulty nutrition is the factor that controls anemia in many of these patients. It remains to be proved, therefore, whether infestation due to hookworm is in itself capable of producing anemia.

Anemia Associated with Miscellaneous Conditions—The cases included in this group are summarized in table 9. A few of them may be discussed in detail.

Malaria The anemia resulting from malarial infection may be extreme and is usually due to a destruction of red blood cells. In most instances there is an increase in the reticulocytes, and Yang and Berglund²⁶ discussed the relationship between a hemolytic process and the response of the reticulocytes in this and other forms of anemia due to excessive destruction of blood. Some observers, notably Seyfarth,²⁷ called attention to the diagnostic significance of an increased reticulocyte count in the anemia due to malaria. We have studied three patients with

23 Dock, G., and Bass, C. C. Hookworm Disease, St. Louis, C. V. Mosby Company, 1910. Keefer, C. S., and Yang, C. S. The Value of Liver and Iron in the Treatment of Secondary Anemia, *J. A. M. A.* **93**: 575 (Aug. 24) 1929. Kobayashi, Toshiyo. Sur les phénomènes régénératifs des hématies dans les anémies de l'ankylostomiase, *Sang* **2**: 129, 1929.

24 Day, H. B., and Ferguson, A. R. The Treatment of Ankylostoma Anemia, *Lancet* **2**: 82, 1914.

25 Schapiro, L. Hookworm Infestation in an Indian (Guaimi) and Non-Indian Population of Panama, *Am. J. Trop. Med.* **10**: 365, 1930.

26 Yang, C. S., and Berglund, H. Differences in Reticulocyte Behavior in Anemia from Malaria and in Pernicious Anemia, *Proc. Soc. Exper. Biol. & Med.* **26**: 417 (March) 1929.

27 Seyfarth, C. Experimentelle und klinische Untersuchungen über die vital-farbbaaren Erythrozyten, *Folia haemat.* **34**: 7, 1927.

severe anemia due to malaria, and in each case there was an increase in the reticulocytes before treatment with quinine was given, and recovery occurred promptly following the cure of the malaria. There are cases, however, in which the period of recovery may be slow, but in these the malarial infection is usually complicated by infestation due to hookworm and by malnutrition²⁸

TABLE 9—*Anemia Associated with Miscellaneous Conditions*

Case	Diagnosis	Red Blood Cells, Millions		Hemoglobin, per Cent		Reticuloocytes, per Cent		Treatment
		Before Treat- ment	After Treat- ment	Before Treat- ment	After Treat- ment	Before Treat- ment	After Treat- ment	
97	Malaria	0.88	4.13	25	82	23.0		Quinine
98	Malaria	2.0	4.5	40	85	11.5		Quinine
99	Malaria	2.7	4.43	50	80	7.2	8.0	Quinine
100	Chlorosis	4.0	5.0	55	85	0.0	7.0	Iron
101	Chlorosis	3.8	4.0	35	65	0.0	2.0	Iron
102	Chlorosis	4.75	5.25	50	75	0.0	2.0	Iron
103	Chlorosis	5.0	5.0	50	85	0.0	6.0	Iron and liver
104	Anemia five years after splenectomy	3.76	5.47	33	86	0.0	8.0	Iron
105	Anemia following splene- ctomy	2.5	5.0	50	80	0.0	8.0	Iron
106	Splenic anemia	3.52	3.78	52	51	1.0	5.8	Liver
107	Splenic anemia	2.25	3.4	50	65	8.0	8.0	Iron
108	Anemia following splene- ctomy	3.5	4.1	52	60	0.0	5.0	Spontaneous
109	Splenic anemia	3.5	4.0	50	60	0.0	5.0	Spontaneous
110	Chronic nephritis	2.27	2.9	43	58	0.0	3.0	Cod liver oil diet*
111	Tuberculosis of intestines, keratomalacia	1.39	1.70	29	38	3.3	14.4	Liver extract, cod liver oil, iron
112	Tuberculosis of intestines	3.08	4.22	58	81	0.6	2.2	Liver and iron, transfusion
113	Tuberculosis of intestines	3.33	3.24	52	48	0.0	3.6	Liver and iron
114	Tuberculosis of intestines	2.76	3.33	43	52	0.6	4.0	Liver and iron
115	Aplastic anemia	1.28	1.95	28	42	0.4	2.4	Liver and iron
116	Aplastic anemia	1.24	1.20	31	30	0.2	3.8	Liver and iron
117	Pernicious anemia	2.02	3.94	50	82	0.0	5.0	Liver extract
118	Pernicious anemia	1.5	4.0	35	80	0.0	15.0	Liver extract
119	Syphilis	2.23	3.32	30	49	4.0	4.0	Iron
120	Pellagra, syphilis	3.09	3.5	58	68	1.0	3.6	Iron
121	Syphilis	3.89	3.8	52	66	0.0	20.0	Iron*
122	Typhoid fever	3.19	4.52	58	86	3.4	9.2	Liver and iron
123	Cirrhosis of liver	3.36	3.59	45	60	1.2	1.8	Liver
124	Acute leukemia	1.18	1.23	29	29	0.4	5.8	Liver and iron
125	Purpura hemorrhagica	3.3	5.2	63	90	1.8	8.1	Transfusion
126	Cancer of stomach	2.5	2.25	50	52	2.0	2.2	Liver extract

* The patient died

Chlorosis There were four female patients with a chlorotic type of anemia who recovered promptly following the exhibition of iron. The cause of these anemias was unknown, but we felt that relative starvation with respect to iron over a long period of time was probably responsible for them. Two of the patients had gastric anacidity. It is well to remember that there is a small but definite group of cases of the

28 Darling, S. T., Barker, M. A., and Hacker, H. P. Hookworm and Malaria Research in Malaya, Java and Fiji Islands. Report of Uncinariasis Commission to Orient, 1915-1917, New York, Rockefeller Foundation, International Health Board, 1920, publication 9.

simple type of anemia resembling the so-called chlorosis which occurs in both sexes, is associated with gastric anacidity, occurs at all ages, has a tendency to recur, and is improved by giving large doses of iron. Such cases have been adequately described by Faber and Gram²⁹. Mettier and Minot³⁰ also described cases of chlorotic anemia associated with disturbances in gastric secretion responding to iron therapy. In many of these patients the dietary habits are of importance. Some of them show an increase in reticulocytes during recovery, and we have noticed that this response is more marked if there is an increase of the total red cell count as well as of the hemoglobin.

Splenic Anemia One patient, who had had a splenectomy five years before coming under observation a second time, was observed with a chlorotic type of anemia which improved following the administration of iron (case 103). The spleen had been removed on account of splenomegaly with leukopenia and anemia. This patient had remained well until shortly before the second admission to the hospital. At the time of her readmission, gastric anacidity was present and disappeared following recovery from the anemia.

This observation was of interest to us in view of some of the cases of so-called splenic anemia reported by Hanrahan³¹. He pointed out that splenectomy was only of temporary therapeutic value in many patients with this syndrome, and that anemia recurred in a number.

There were two other patients who had had a splenectomy for splenic anemia and showed no improvement of the anemia following this procedure. Three other patients with a similar syndrome were given liver or iron. No improvement followed the feeding of liver in one, and only slight improvement followed the use of iron in the other two.

Tuberculosis of the Intestines In a previous communication by Keefer, Huang and Yang³² it was pointed out that the patients with intestinal tuberculosis of the ulcerative type and anemia were those who had diarrhea or constipation alternating with diarrhea. It was concluded that the process interfering with nutrition, together with the disturbances in appetite, probably accounted for the anemia. When similar patients were given liver and iron, no improvement of the anemia occurred. The improvement in case 112 was due to a transfusion of blood.

In our experience, no improvement of the anemia was observed when liver and iron were exhibited to patients with aplastic anemia, acute

29 Faber, K., and Gram, H. C. Relations Between Gastric Achylia and Simple and Pernicious Anemia, *Arch. Int. Med.* **34** 658 (Nov.) 1924.

30 Mettier, S. R., and Minot, G. R. The Effect of Iron in Blood Formation as Influenced by Changing the Acidity of the Gastric Contents in Certain Cases of Anemia, *J. Clin. Investigation* **7** 510, 1929.

31 Hanrahan, E. M. Splenic Anemia. A Study of End-Results with and without Splenectomy, *Arch. Surg.* **10** 639 (March) 1925.

32 Keefer, Huang and Yang (footnote 18 first reference).

leukemia, cirrhosis of the liver, anemia associated with syphilitic infection or chronic nephritis

The patient who developed anemia following typhoid fever without hemorrhage was interesting in that he was unable to take large amounts of food during the course of his illness because of vomiting and the presence of a persistent diarrhea associated with an amebic dysenteric infection. As a result anemia and edema developed late in the course of the disease, and the patient recovered from both conditions when he was able to take an adequate diet.

Nothing has been added to our knowledge of the anemia of typhoid fever since Thayer's³³ complete review of the subject a number of years ago. Its cause is obscure although Longcope³⁴ described changes of an aplastic nature in the bone marrow of these patients. When one studies the cases of patients with typhoid fever who have been treated by the administration of large amounts of food instead of by the method of starvation during the course of the disease, anemia without intestinal hemorrhage is infrequently observed.³⁵ Many of the complications described in the older literature as occurring during typhoid fever, such as anemia, polyneuritis, transitory ascites and the various ocular complications, should be reviewed in the light of our present knowledge regarding the influence of malnutrition in producing such changes in the tissues.

RESULTS OF TREATMENT

The results obtained with various forms of treatment are summarized in chart 3. It is clear that conspicuous increases in the regeneration of the hemoglobin were obtained in many cases with various forms of therapy, and it is also evident that no demonstrable effect was obtained in other cases following the same form of treatment. The most striking results were seen after the administration of iron or of liver supplemented with iron. From the chart it appears that the results obtained following the administration of iron were as noticeable as those following the administration of liver and iron. In some cases this was true. However, when individual cases were studied it could be shown without doubt that the regeneration of the hemoglobin was greater in some cases following the exhibition of liver and iron than when either was given alone. This is illustrated in chart 4. It is obvious from these cases that if the regeneration of hemoglobin were occurring following the use of liver

33 Thayer, W. S. Two Cases of Post-Typhoid Anemia, Johns Hopkins Hosp. Rep. 4 83, 1894, Observations on the Blood in Typhoid Fever, Bull. Johns Hopkins Hosp. 8 47, 1899.

34 Longcope, W. T. The Bone Marrow in Typhoid Fever, Bull. Ayer Clin. Lab., Pennsylvania Hosp. 2 1, 1905.

35 Zia, S. H. Typhoid Fever. A Clinical Study of 256 Cases in Peking, Nat. M. J., China 14 105, 1928.

diets and in some of the anemias associated with pregnancy, infestation due to hookworm and with dysentery. We have not been able to demonstrate that it is potent in increasing the regeneration of hemoglobin in patients with anemia associated with tuberculosis of the intestines and diarrhea, nor in aplastic anemia, the anemia of kala-azar and other anemias when complicated by intercurrent infections. The daily rate of

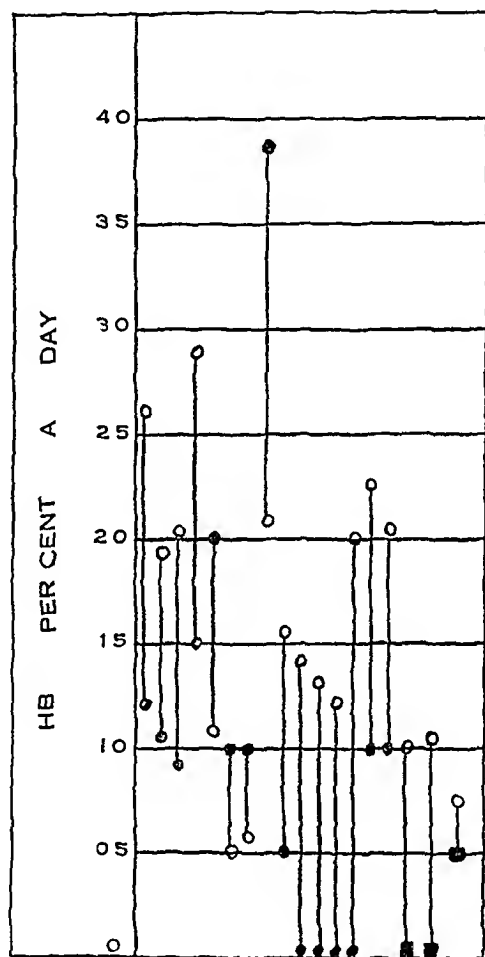


Chart 4—This chart illustrates the regeneration of the hemoglobin in patients (each line represents an individual patient) who received liver and then liver and iron. The solid dots represent the response to liver and the circles the results when iron was added. In some cases iron was given before liver was added. The squares indicate the response following the administration of liver extract. It is apparent that in some cases combinations of liver and iron are more effective than either one alone.

the regeneration of hemoglobin that we have observed following liver therapy in all forms of anemia is summarized in chart 3.

The results of feeding liver in the various anemias are in agreement with the observations of other observers, and the question has been subjected to a critical review by Vaughan¹³. She pointed out that

treatment with liver was most effective in pernicious anemia and in some of the anemias associated with pregnancy and so-called sprue. She also stated that it was potent in posthemorrhagic anemia and some of the obscure nutritional anemias. From her observations and the review of the reported cases, she concluded that liver was probably most effective in the anemias associated with a hyperplastic bone marrow, but the reason for its ineffectiveness in other cases was not clear. It is evident, therefore, that liver is of value in the treatment for some forms of anemia, but it cannot be denied that it is of no demonstrable value in the treatment for others. This is the experience of all observers. These failures have been attributed to various factors, such as the presence of infection, the feeding of insufficient quantities of liver, or giving it over too short a period of time, or to a difference in the fundamental disturbance that exists in the different anemias. There is considerable evidence that all of these factors are of importance in explaining many of the failures observed. To give better correlation, we shall review this evidence briefly.

It will be admitted generally that many infections cause increased destruction of blood cells and also inhibit the formation of blood. The explanation for this phenomenon is not clear. There are certain infections, however, in which an anemia may be improved following the use of liver or liver extract, in spite of the persistence of infection. We observed such responses in some patients with anemia associated with chronic dysentery, so that infection may be only one factor in explaining the inhibition of the formation of red cells when it is associated with an anemia. We demonstrated that other factors such as deficient diets are of importance in many such cases.

Besides the inhibitory effect of infection on the formation of blood following the administration of liver, it has been stated that the failure to observe positive responses is due to the feeding of inadequate amounts of liver over too short a period of time. At the present time, the amount of liver that is necessary for the maximum output of hemoglobin in the forms of anemia in which it is effective is unknown. It is to be noted, however, that at least 300 or 400 Gm must be given daily and for a period of at least two weeks before a failure can be recorded. While it is undoubtedly true that inadequate doses of liver may account for many of the observed failures, it is not the case in all, because we have observed negative responses to liver therapy when the dose has been large, but positive responses in the same patients when iron was given. While it would appear that infection and inadequate dosage of liver are responsible for some of the failures observed, there remain other factors which are incompletely understood.

The most likely explanation for this varying response is the difference in the fundamental disturbance existing in different anemias. It is now

evident from the experimental work of Whipple and Robscheit-Robbins, and others, that there are a number of factors which influence the regeneration of the blood, and a disturbance of one or more of these factors will result in anemia. These observations are being confirmed in the anemias in man as information accumulates. In discussing the fundamental differences existing in some of the anemias, such as pernicious anemia, which responds in a spectacular way to the feeding of liver, and other forms of anemia which do not show such remarkable improvement, Whipple, Robscheit-Robbins and Walden³⁷ advanced the following points. In pernicious anemia there is a faulty construction or a lack of the constituents that form the stroma of the red cells, and no deficit of the hemoglobic pigments. When liver is fed to these patients, the missing element necessary for the maturation of red cells and the constituents that form stroma of the red cells are supplied, and recovery occurs promptly. In the case of the so-called "secondary" anemias, they postulate that there is a deficit of pigment-producing substances of which there are organic and inorganic elements, and recovery in these anemias will not occur until these substances are supplied in the diet. In other words, they are of the opinion that both pernicious anemia and many of the so-called secondary anemias are due to a deficiency of substances necessary for the formation of red cells and hemoglobin, and recovery will not occur until the necessary substances are supplied. If one accepts the fact that the liver and the kidney supply a maximum amount of substances most suitable for the formation of red cells and hemoglobin, and that both forms of anemia mentioned are due to a deficiency of these substances, it is difficult to understand why spectacular results do not occur in all cases of anemia when liver is fed. The explanation offered by Whipple, Robscheit-Robbins and Walden³⁷ is that it is difficult for patients with secondary anemias due to lack of pigment-producing substances to take the required amount of liver which produces spectacular results. In other words, it is a matter of quantitative factors, and it would appear that the liver and the kidney contain more stroma-building substances than pigment-building materials.

In the main, we are in agreement with these conclusions and feel that the explanation offered for the difference in response to liver serves as an excellent working hypothesis in the study of the various anemias in man. Certain facts, however, are of importance. First of all, if one excludes the cases in which there are factors inhibiting the effect of liver, such as infection or damage to the bone marrow, there remain other cases which fail to respond to liver but respond to iron. On the other hand, in other patients with secondary forms of anemia the

37 Whipple, G. H., Robscheit-Robbins, F. S., and Walden, G. B. Blood Regeneration in Severe Anemia. Liver Fraction Potent in Anemia Due to Hemorrhage, *Am J M Sc* **179** 628 (May) 1930.

response to liver may be as spectacular as that observed in pernicious anemia, and improvement may occur rapidly. As a result of these observations, it has been pointed out previously that some of the clinical anemias were probably due to a lack of iron, whereas others were due to a lack of substances found in the liver or the kidney, and in still others both substances were lacking. If these ideas were expressed in the terms used by Whipple and Robschey-Robbins, it would be stated that in some anemias, the deficiency is due to a lack of stroma-building substances (pernicious anemia), in others to a lack of pigment-building materials, and in others, to a lack of both stroma-building and pigment-building substances.

One of the difficulties in drawing conclusions from any clinical study at the present time lies in our lack of information regarding quantitative factors and in our inability to classify the anemias in man in any way other than by the results obtained following treatment. It is impossible to predict in a given case whether the anemia will respond to liver alone, iron alone, or to a combination of both. Further study is needed before these questions can be settled.

The Value of Iron—It is now generally acknowledged that iron is potent in increasing the regeneration of the hemoglobin in many forms of anemia. The experimental evidence supporting this statement was reviewed recently by Robschey-Robbins³⁸. Whipple and Robschey-Robbins³⁹ designated the response obtained by iron and certain other metals such as copper as the "salt effect," and they found that the maximum output of hemoglobin may be observed in dogs after feeding 60 mg of iron a day and that additional amounts of iron do not cause an increased output of hemoglobin.

The recent studies of Mettler and Minot,⁴⁰ and Keefer, Huang and Yang⁴¹ indicated that iron is of value in the treatment for many of the chlorotic types of anemia, posthemorrhagic anemias, some of the anemias due to malnutrition, pregnancy and infestation produced by hookworm. The dose of iron that produces the maximum output of hemoglobin in man, when it is effective, is unknown. We were able to show that a positive effect could be produced in some patients by 90 mg a day, but at that time we did not have a sufficient number of observations

38 Robschey-Robbins, F. S. Regeneration of Hemoglobin and Erythrocytes, *Physiol Rev* **9** 666, 1929.

39 Whipple, G. H., and Robschey-Robbins, F. S. Blood Regeneration in Severe Anemia. XVI. Optimum Iron Therapy and Salt Effect, *Am J Physiol* **92** 362, 1930.

40 Mettler, S. R., and Minot, G. R. The Effect of Iron on Blood Formation as Influenced by Changing the Acidity of the Gastric Contents in Certain Cases of Anemia, *J Clin Investigation* **7** 510, 1929.

41 Keefer, C. S., Huang, K. K., and Yang, C. S. Liver Extract, Liver Ash, and Iron in the Treatment of Anemia, *J Clin Investigation* **9** 533, 1930.

to determine the minimum effective dose of iron in the various anemias. It was clear, however, that the optimum dose of iron varied in different forms of anemia so that if a positive effect is to be obtained large doses must be given.

When a positive effect was obtained following the administration of iron, the reticulocytes usually increased. In most cases, the increase at the peak of the rise was inversely proportional to the total number of red cells present before the beginning of treatment. There were exceptions to this rule, but they were observed usually in patients whose blood showed a low color index.

The Value of Liver Ash—The inorganic constituents of liver, when given in the form of liver ash, have been found to be effective in increasing the regeneration of hemoglobin and red cells in dogs with posthemorrhagic anemia, and in the nutritional anemia of rats. Elden and McCann⁴² reported the preliminary phenomenon of a remission when it was exhibited to a patient with pernicious anemia, but complete recovery did not ensue until liver extract (Lilly, no 343) was given. A small group of ten patients with anemia was studied following feeding with liver ash. It was given in amounts equivalent to 300 Gm of whole liver a day, and on chemical analysis this amount contained 21 mg of iron.

The results following the use of liver ash were never striking, but when the same patients were given iron in the form of ferrous carbonate in doses ranging between 90 and 480 mg a day, a positive effect could be demonstrated by an increase in the reticulocytes and in the rate of the regeneration of the hemoglobin.

The results are summarized in chart 5. It is certain that iron was more efficacious than the liver ash.

The reason for our failure to observe positive effects following the use of liver ash was probably due to the small amount of iron contained in it, since we have shown that positive effects from iron therapy may be obtained in some patients with 90 mg or more a day.

The Value of Liver and Iron—The results obtained in the regeneration of hemoglobin following the use of liver and iron are plotted in chart 3. It may be observed that the results obtained from the feeding of iron were as striking as those obtained following the administration of liver and iron, and in many cases this was true. However, because many of these patients received liver and iron together from the beginning of the observations it was impossible to separate the effect of the iron from that of the liver, and the results are misleading. In the cases in which the effect of the iron could be separated from that of

⁴² Elden, C. A., and McCann, W. S. Effect of Ash of Liver on Blood Regeneration in Pernicious Anemia, *Proc Soc Exper Biol & Med* **25** 746 (June) 1928.

the liver, due to the fact that each substance was given alone for a period of time varying from ten to fourteen days, it was shown that the effect of liver could be enhanced by iron. This was illustrated in chart 4. It may be seen that in many cases the results were more striking following both than when either was given alone. In some instances there was no response following the ingestion of liver, but an excellent response following iron.

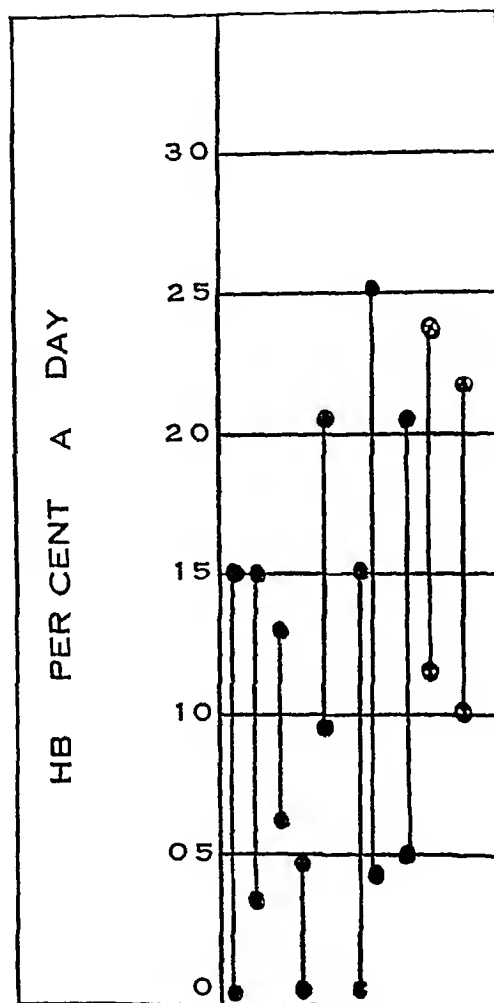


Chart 5—This chart illustrates the difference in the regeneration of the hemoglobin following treatment with liver ash and iron. The lower dots represent the daily rate of regeneration of the hemoglobin following the administration of liver ash in amounts equal to 300 Gm of whole liver. This amount contained 21 mg of iron. The upper dots represent the response following larger doses of iron. The two cases at the extreme right illustrate the difference in regeneration of the hemoglobin following 180 mg and 480 mg of iron a day.

It is evident, therefore, that in some anemias, at least, liver and iron given in combination are more effective than when either one is given alone. There are other cases in which the maximum effects may be obtained with iron alone or liver alone.

Value of Liver Extract and Iron—What we have said regarding whole liver and iron also applies to liver extract and iron. That is to say, in some cases, maximum responses may be obtained with liver extract and iron, and in others with iron alone. We have found liver extract potent in some of the nutritional anemias of childhood, in some anemias associated with chronic dysentery, pregnancy and infestation due to hookworm. It has been of little demonstrable value in posthemorrhagic anemia.

THE RESPONSE OF THE RETICULOCYTES

One of the best methods of determining the activity of the bone marrow and the efficiency of any form of treatment for the various anemias is the study of the response of the reticulocytes. Minot and Murphy⁴³ first emphasized this method of study in evaluating treatment with liver in pernicious anemia, and later the same method was used in testing the potency of liver extract in the same disease. They found that the height of the increase in reticulocytes depended on the level of the red cell count and the dosage of liver extract. That is to say, the lower the red count before treatment and the larger the dose of liver or liver extract, the higher the reticulocytes increased at the peak of the rise.

In a previous study of fifty-eight cases of secondary anemia, we⁴⁴ found that the increase of the reticulocytes varied with the type of treatment, the level of the red blood count before treatment was begun and the cause of the anemia.

The reticulocyte responses observed in the present cases have been tabulated in the tables and summarized in charts 6 and 7. Chart 6 illustrates the highest reticulocyte count observed in all of the cases when plotted against the number of red blood cells before the beginning of therapy. Chart 7 illustrates the highest number of reticulocytes observed in the patients who recovered regardless of the treatment employed. It appears from this chart that the lower the red blood count before the beginning of treatment, the greater the reticulocyte response during recovery. There are, however, a number of exceptions to this statement which require further comment.

In the posthemorrhagic anemias, increases in the reticulocytes were not observed following the ingestion of liver extract, and in some cases the reticulocytes did not increase following transfusions of blood. In

43 Minot, G. R., and Murphy, W. P. Treatment of Pernicious Anemia by a Special Diet, *J. A. M. A.* **87** 470 (Aug. 14) 1926, A Diet Rich in Liver in the Treatment of Pernicious Anemia, *ibid.* **89** 759 (Sept. 3) 1927.

44 Yang, C. S., and Keefer, C. S. The Response of the Reticulocytes in Secondary Anemias Following Various Forms of Treatment, *Arch. Int. Med.* **45** 456 (March) 1930.

one case, iron, and in another, liver and iron, caused no increase in spite of recovery. In others, the reticulocytes increased during recovery following the administration of liver and iron, the transfusion of blood, or the use of iron alone.

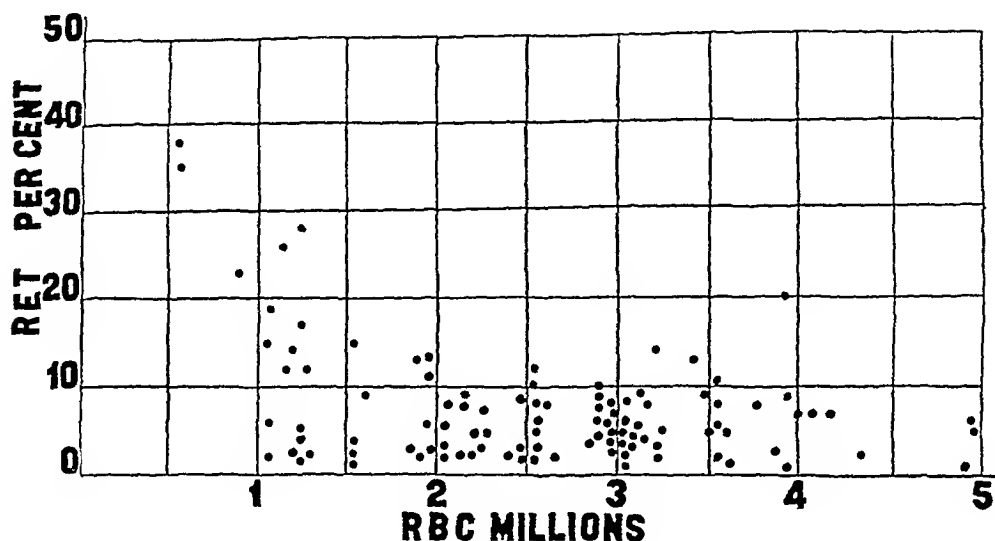


Chart 6—The reticulocytes at the peak of the rise in all patients regardless of whether or not they recovered

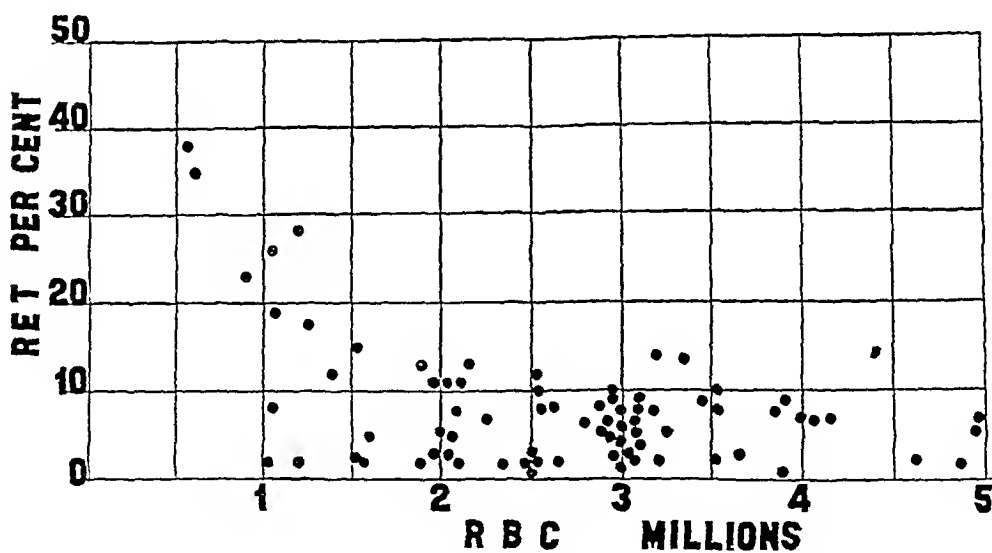


Chart 7—The reticulocytes at the peak of the rise in the patients who recovered

In the cases of anemia resulting from chronic dysentery, slight responses were observed in some patients following transfusion, or when the recovery occurred slowly without any special therapy, or when no improvement was observed due to the severity of the infection. In the cases in which prompt recovery from the anemia followed adequate diets or special therapy such as the administration of liver and iron, the reticulocytes were increased.

In the anemias resulting from malnutrition, from infestation due to hookworm and from pregnancy, increases in the reticulocytes were observed regularly except when transfusion of blood was employed, or when the recovery was slow

In kala-azar, the increase in reticulocytes during recovery was slight except in two patients who had comparatively recent infections. These observations illustrate that when there are pathologic processes in the bone marrow, such as those observed in kala-azar, the reticulocytes may not appear in the circulating blood in greater numbers

In the cases listed under miscellaneous anemias, increases were noted when recovery occurred, but were usually only slight when no improvement was observed. Occasionally conspicuous increases in the reticulocytes were seen without any improvement in the anemia. In these cases, there was usually a severe infection such as tuberculosis of the intestine which was fatal

In summary, then, our experience has shown that the reticulocytes may increase during recovery from many forms of anemia, and that the more severe the anemia, the higher the reticulocyte count at the peak of the rise. On the other hand, increases in the reticulocytes may not be observed following transfusion of blood, or in cases in which there is a disorder of the bone marrow such as occurs in kala-azar. In patients with a low color index there may be no increase in the reticulocytes if recovery is slow, and the erythrocyte count remains stationary. If, on the other hand, there is an increase of both the erythrocytes and the hemoglobin during recovery, the reticulocytes may increase. Furthermore, if the reticulocytes have increased to a maximum before treatment is begun, a further rise may not be observed. Similar observations have been made by Minot and Murphy in patients with pernicious anemia.

SUMMARY AND CONCLUSIONS

In a study of the treatment in 126 cases of anemia due to various causes, the following facts were evident

- 1 The recovery from anemia due to chronic loss of blood may be accelerated following the administration of liver and iron. In some cases, transfusion of blood was necessary owing to the severity of the anemia. Continued loss of blood in small amounts and sepsis retard recovery.

- 2 Anemias resulting from inadequate or faulty diets were often associated with the avitaminoses or other deficiency disorders. Many of these patients recovered following a well balanced diet and in some regeneration of the hemoglobin was accelerated by the use of liver or iron.

3 The anemia associated with chronic dysentery usually appeared in patients who had been on inadequate diets, and who had had active dysentery for two months or longer. Hemorrhage, infection and gastric anacidity played a minor rôle in the production of the anemia. In the group as a whole, all of the clinical features that are said to be characteristic of pernicious anemia were observed, including atrophy of the lingual papillae, subacute combined sclerosis, gastric anacidity and anemia responding to liver extract. These observations lend support to the hypothesis that pernicious anemia is a deficiency disease.

4 Anemia associated with infestation due to hookworm may be cured with iron, or liver and iron, while the patients continue to carry the worms. Malnutrition and faulty diets are important factors in predisposing such patients to anemia.

5 Women with the anemias of pregnancy recover following the transfusion of blood or following the administration of liver and iron. In some cases, iron alone is positive, in others, liver or liver extract is potent in increasing the rate of recovery.

6 Recovery from the anemia associated with kala-azar may be extremely slow in spite of treatment with antimony compounds, transfusions of blood and ingestion of liver and iron. In this condition it appears as if the damage to the bone marrow were responsible for the anemia.

7 When recovery occurred in many of the foregoing types of anemia, the reticulocytes were increased. Generally speaking, the number of reticulocytes depends on the level of the red cell count at the beginning of the treatment, although there were exceptions in cases in which one observed relatively large increases in reticulocytes with a high red blood cell count. In most of these cases the hemoglobin content was low. In other cases an increase in the reticulocytes was not observed following treatment. In some of these cases the reticulocytes had been increased before treatment was begun, in others, they were never increased.

8 When liver ash was given in amounts equivalent to 300 Gm. of whole liver a day, containing 21 mg. of iron, striking results were not observed. In several instances, there was a moderate increase in the hemoglobin, red blood cells and reticulocytes, and this response was usually observed in patients who subsequently recovered promptly on larger doses of iron.

9 In some cases of anemia, liver and iron were more effective than when either one was given alone. In others, the maximum effect was observed following the use of iron.

10 Liver extract was of demonstrable value in some of the nutritional anemias of childhood, some of the anemias associated with preg-

nancy and in chronic dysentery. It was of little value in posthemorrhagic anemia.

11 From our observations, it was not possible to predict in every case which form of treatment would be most beneficial. If complete recovery is not observed in patients following the use of iron, liver should be added. In many patients who do not respond to liver or iron, there is usually an adequate cause to explain their failure. Infection and pathologic processes of the bone marrow are of the greatest importance. The response in the various clinical anemias following the ingestion of food substances other than liver, kidney or iron needs further investigation.

METABOLISM IN MYOTONIA ATROPHICA

REPORT OF A CASE¹

SERGIUS MORGULIS, PH D

AND

ALEXANDER YOUNG, M D

WITH THE ASSISTANCE OF J K MILLER AND E JANICK

OMAHA

Myotonia atrophica or dystrophica is one of the rarer forms of myopathy, which, in addition to the typical myotonia, is characterized by the following conditions (1) onset usually in the third decade, (2) limitation of the myotonia to special groups of muscles, namely, those of the hands, the tongue and the legs, (3) typical distribution of the atrophy to the face, the sternocleidomastoid muscles, the hand and the forearm and the muscles of the leg, (4) general emaciation, (5) baldness, (6) testicular atrophy, (7) cataract, (8) defect in speech, (9) combination with ataxia and Westphal's sign¹

The etiology of this disease is obscure Naegeli² regarded the pathogenesis of the disease as originating in a polyglandular disturbance, presumably with a marked hereditary predisposition This relation to endocrine involvement was also assumed by Barkman³ and others, though the evidence for this is more circumstantial than direct The occurrence of primary cataracts, testicular atrophy or hypogenitalism in the female, together with atrophic changes in the skin, is usually cited as favoring an assumption of glandular disturbance as the basis of this peculiar condition, which manifests itself in an increased and persistent tonus of the flexor muscles, particularly those of the extremities and of the face

REPORT OF A CASE

History—Mr R R, aged 28, who was born in America of Swedish parents, first noted the development of progressive muscular weakness following an inguinal herniotomy on the left side, which was performed in 1926 This operation was followed by atrophy of the left testis When the patient entered the University Hospital in February, 1930, the musculature in the limbs and also in the face and neck was greatly reduced, giving him the typical "hatchet face," "polelike neck" and "pipestem extremities" of patients with myotonia He had lost the knee

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¹ From the Department of Biochemistry and the University Hospital University of Nebraska College of Medicine

1 Curschmann, H Deutsche Ztschr f Nervenhe 45 161, 1912

2 Naegeli Munchen med Wchnschr 64 1631, 1917

3 Barkman, A Acta med Scandinav 56 686, 1922

jerk, and the atrophy of the legs was advanced far enough to produce drop foot and the characteristic steppage gait. The ability to relax the muscles was considerably diminished, which was well shown in the difficulty he experienced in letting go after gripping something with his hand.

He had lost only about from 7 to 8 pounds (3.2 to 3.6 Kg). The Wassermann test gave negative results, and the past history was unimportant, except for some diseases of childhood, influenza and a mild attack of smallpox in 1918. The family history gave no evidence of a possible hereditary etiology.

Ophthalmoscopic examination showed fine opacities in the lens, more marked at the periphery. Examination of the blood showed 4,680,000 red cells, 7,000 white cells and 85 per cent hemoglobin. Studies on the basal metabolism repeated on two occasions showed rates of -13 and -14 per cent, respectively.

Urinalysis gave negative results for albumin and sugar.

The analysis of the blood made on two different occasions gave the results shown in table 1.

In addition to the determinations made on the whole blood, the calcium serum was found to be 11 mg per hundred cubic centimeters and the inorganic phosphorus, 3.5 mg.

TABLE 1—*Results of Analysis of the Blood of a Patient with Myotonia Atrophica*

	First Analysis, Mg per 100 Cc	Second Analysis, Mg per 100 Cc
Nonprotein nitrogen	39.0	34.0
Sugar	90.0	
Creatinine	1.5	1.7
Creatine		4.2
Uric acid		4.4
Lactic acid		36.9

In view of the fact that even mild excitation would cause the lactic acid of the blood to rise above the normal level, nothing in the chemical picture of the blood of the patient threw any light on the pathogenesis of the condition.

For nearly a month the patient was kept on a carefully controlled diet during which the creatine-creatinine excretion was studied.⁴ The specimens of urine were collected for every twenty-four hours and preserved with thymol. The specimens were analyzed for the total content of nitrogen, creatinine, creatine and uric acid. Organic acids were determined by the Van Slyke-Palmer method and also by the recent modification of this procedure by Greenwald.⁵

The diet specially prepared in the kitchen of the hospital was selected so that equilibrium in the nitrogen content was maintained throughout the experiment, and the patient retained his weight of 57 Kg unchanged. This diet, consisting of about 60 Gm of protein, 160 Gm of carbohydrate and 120 Gm of fat, furnished about 2,000 calories daily. The protein was given largely (60 per cent) as meat, but during some periods this was replaced by eggs and cheese in equivalent amounts. During one period, this moiety of the protein was furnished by gelatin.

The results of this metabolic study are summarized in table 2. The excretion of nitrogen was fairly constant from day to day, and, except during the days

⁴ Miss Fritschel, the dietitian, personally supervised the patient's dietary throughout the whole experiment.

⁵ Greenwald I. J. Biol. Chem. 85:447, 1930.

TABLE 2—Results of Study on Metabolism Made on a Patient with Myotonia Atrophica

Date	Duration of Period, Days	Total Output of Urine, Gm	Daily Urinary Excretion, Gm				Nitrogen Partition, in per Cent of Total			Percentage of Total			Total-Nitrogen if Organic Acid CC		Comment
			Total Nitrogen	Creatinine	Creatinine	Creatinine	Creatinine Nitrogen	Creatinine Nitrogen	Creatinine Nitrogen	Creatinine Nitrogen	Creatinine Nitrogen	Creatinine Nitrogen	Creatinine Nitrogen		
March 10-13	3	2,830	7.87	0.795	0.703	1.198	0.909	3.73	3.30	3.85	16.9	291	225	150 Gm of carbohydrate, 119 Gm of fat and 62 Gm of protein (36 Gm of meat protein)	
March 13-16	3	3,850	6.32	0.725	0.562	1.287	0.703	3.70	3.28	3.70	13.7	371	272	153 Gm of carbohydrate, 120 Gm of fat and 60 Gm of protein (no meat protein)	
March 16-19	3	3,860	7.19	0.717	0.553	1.070	0.710	3.69	1.91	3.30	33.0	317	262	163 Gm of carbohydrate, 120 Gm of fat and 59 Gm of protein (no meat protein)	
March 19-22	3	2,950	6.91	0.775	0.595	1.370	0.667	3.77	4.12	3.20	13.4	291	210	167 Gm of carbohydrate 118 Gm of fat and 62 Gm of protein (36 Gm of meat protein)	
March 22-23	1	1,570	6.28	0.965	1.390	2.355	0.880	5.67	8.17	4.67	61.2	295	273	192 Gm of carbohydrate, 121 Gm of fat and 65 Gm of protein (31 Gm of meat protein)	
March 23-24	1	1,000	5.16	0.788	1.312	2.130	0.900	5.63	9.60	5.81	63.0	273	266	160 Gm of carbohydrate, 121 Gm of fat and 60 Gm of protein (35 Gm of meat protein)	
March 24-25	1	1,220	6.85	1.031	1.601	2.632	0.880	5.55	8.77	1.28	60.8	270	259	161 Gm of carbohydrate, 121 Gm of fat and 62 Gm of protein (31 Gm of meat protein)	
March 26-29	3	2,750	6.51	0.769	0.158	1.227	0.903	1.31	2.58	1.61	37.3	310	287	161 Gm of carbohydrate 121 Gm of fat and 63 Gm of protein (36 Gm of meat protein)	
April 1-3	2	2,100	7.89	0.810	0.608	1.118	0.831	3.93	2.81	3.53	12.0	339	303	165 Gm of carbohydrate 121 Gm of fat and 61 Gm of protein (35 Gm of meat protein)	
April 3-6	3	3,210	8.28	0.615	0.533	1.178	0.673	2.97	2.88	2.71	15.3	310	288	161 Gm of carbohydrate 122 Gm of fat and 61 Gm of protein (no meat protein)	
April 6-8	2	2,115	7.58	0.515	0.565	1.383	0.915	3.97	2.77	1.17	11.0	332	238	161 Gm of carbohydrate 123 Gm of fat and 63 Gm of protein (36 Gm of meat protein)	

when creatine was administered, the amount averaged about 7.3 Gm. During the twelve days of the preliminary study (fore-periods), though during half of this time no meat was consumed, the output of creatinine nitrogen was practically unchanged, constituting about 37.2 per cent of the total urinary nitrogen. The average daily excretion of creatinine was 0.753 Gm. During the last ten days of the experiment (after-periods), the daily variations were somewhat greater, but the creatinine nitrogen still constituted 37.8 per cent of the total excretion of nitrogen. The creatinine coefficient of our patient, being 13.4 mg. per kilogram of weight, is definitely low for the age of the patient and approaches more nearly that of a child. However, the patient showed persistent creatinuria and, if the total elimination of creatinine is taken into consideration, the total daily excretion of 23 mg. per kilogram of body weight is an entirely normal coefficient for a person of that age. Therefore, it would seem that the chief abnormality of the creatine-creatinine metabolism of the patient was the inability to convert creatine to creatinine. Thus, part of the creatine, about 43 per cent, appeared in the urine unchanged, but the metabolism of the total amount of creatine was not appreciably affected.

The exogenous origin of some of the urinary creatine is obvious when one compares the results of a diet in which meat was the essential source of protein with those of a diet in which creatine-free foods were substituted for the meat. The decrease in the creatinuria during the second, and especially during the third, fore-period is notable. However, the feeding of a protein rich in arginine (gelatin), which was done in the period from April 3 to April 6, had no influence on the output of either creatinine or creatine, which had actually diminished during that period.

Having established definitely during a preliminary study extending over twelve days the creatine-creatinine excretion of the patient, we gave him 1.32 Gm. of creatine-hydrate, equivalent to 1 Gm. of creatinine, by mouth on three consecutive days. The excretion of creatine on those days was greatly increased, constituting nearly 62 per cent of the total creatinine content in the urine. During the first day, 1.049 Gm. of extra creatinine was excreted in the urine, of which 20 per cent was in the form of extra preformed creatinine. During the second day, for an undetermined cause, unless the reduced output of urine may be considered responsible, only a little more than 80 per cent of the ingested creatine had been eliminated, a much smaller proportion of which (less than 5 per cent) was in the form of extra creatinine. This retention, however, was only temporary and was fully accounted for by the creatine eliminated in the next twenty-four hour period. In this third period, again, about 20 per cent of the total extra excretion was in the form of preformed creatinine. Taking 0.753 Gm. as the average daily excretion of creatinine, the average excretion on the three days when creatine was fed (0.928 Gm.) showed an increase of 0.175 Gm., or 23.2 per cent, per day. The daily excretion of creatine likewise increased from 0.553 Gm. to 1.444 Gm., or 0.891 Gm. The increase in the total excretion of creatinine resulting from feeding creatine equivalent to 1 Gm. of creatinine was thus 1.066 Gm. In other words, the creatine fed is recovered in the urine eliminated within a period of twenty-four hours, whereby 16.6 per cent seems to be converted to creatinine, while 83.4 per cent is eliminated unchanged.

We purposely limited the oral administration of creatine so as not to overtax the organism's ability to metabolize it, but even such a small amount was eliminated practically quantitatively in the course of the day, and had no effect on the creatine-creatinine excretion in subsequent periods. The excretion of uric acid was somewhat increased during the days when creatine was fed. Probably

the most striking effect was shown by the study of the excretion of organic acids. Although the results do not permit us to draw any definite conclusion as to the influence exerted by the feeding of creatine on the absolute amount of organic acid in the urine, a distinct difference appears when the organic acids are determined either by the Van Slyke-Palmer method or by the Greenwald⁵ modification of that method. The results obtained by these two procedures varied considerably. But whereas during the twelve days of the fore-period and the ten days of the after-period the difference in the daily excretion of organic acid, as determined by these two methods, averaged between 78 and 59 cc. of tenth-normal acid, respectively, during the three days when the creatine was fed, the difference was only 13 cc.

COMMENT

The persistent creatinuria observed in our patient is similar to that described in several other cases of myopathy. Levene and Kristeller⁶ found creatinuria in patients with muscular dystrophy, and Bodansky, Schwab and Brindley⁷ in a case of myositis fibrosa. However, Burger⁸ found a much less pronounced creatinuria in his several patients on a strictly creatine-free diet.

In view of the diminution in the excretion of creatinine, the coefficient for creatinine, as observed by Gibson, Martin and Buell⁹ and others, likewise tends to become very low. However, the coefficient for the total creatinine content, as we have determined for our patient, may actually remain normal in spite of the fact that the coefficient for preformed creatinine is unusually low. Indeed, Burger⁸ maintained that the coefficient for the total creatinine content is low only in patients whose musculature is undergoing massive reduction, as in progressive dystrophy, which serves to differentiate this disease from various other types of myopathy in which the coefficient for the total creatinine content remains high or practically normal.

The outstanding fact in this study was the inability of the patient with myotonia atrophica to retain and to store exogenous creatine. In the normal adult, small doses of administered creatine are completely retained, as shown by the work of Folin,¹⁰ Myers and Fine,¹¹ and Rose and Dimmitt.¹² Our patient, however, was unable to retain a similar dose of creatine, and it was eliminated quickly through the urine.

6 Levene, P. A., and Kristeller, L. *Am. J. Physiol.* **24**: 45, 1909.

7 Bodansky, M., Schwab, E. H., and Brindley, P. *J. Biol. Chem.* **85**: 307, 1929.

8 Burger, M. *Ztschr. f. d. ges. exper. Med.* **9**: 361, 1919.

9 Gibson, R. B., Martin, F. T., and Buell, M. *A Metabolic Study of Progressive Pseudohypertrophic Muscular Dystrophy and Other Muscular Atrophies*, *Arch. Int. Med.* **29**: 82 (Jan.) 1922.

10 Folin, O. *Festskr. f. Olof Hammarsten*, Upsala Lakaref. Forh., 1906, pt. 3.

11 Myers, V. C., and Fine, M. S. *J. Biol. Chem.* **21**: 377, 1915.

12 Rose, W. C., and Dimmitt, F. W. *J. Biol. Chem.* **26**: 345, 1916.

This inability to fix creatine has been noted in various conditions involving the muscular system. Thus, Powis and Raper¹³ and Ziegler and Pearce¹⁴ found the same condition in children with amyotonia congenita, Gibson and Martin,¹⁵ in a woman with pseudohypertrophic dystrophy, and Bodansky and his associates,⁷ in a boy 15 years of age afflicted with generalized myositis fibrosa. Present knowledge of the existence in muscle of a labile compound of creatine with phosphoric acid, which hydrolyzes readily in the course of muscular activity and is again resynthesized, and its important rôle in muscular activity suggest that the inability of diseased muscles to retain or even to store temporarily the exogenous creatine may be associated with their inability to form this phosphagen compound.

In our patient the feeding of creatine called forth a definite and considerable rise in the urinary output of creatinine as much as 16.6 per cent of the ingested creatine having been eliminated after conversion to creatinine. It is generally recognized that such conversion takes place in the muscles which suggests, at least as a strong probability, that the mechanism for the creatine-phosphoric acid synthesis and the mechanism for the creatine-creatinine transformation in muscles are independent of each other. In view of the fact that the experimental work from the Meyerhof school has shown that the synthesis of phosphagen is closely tied up with the glycogen metabolism of the muscle it would seem that the inability of the affected muscles to retain creatine is ultimately to be correlated with the more fundamental disturbance in the glucid metabolism and the lack of glycogen.

SUMMARY AND CONCLUSION

1 In a patient with myotonia atrophica, whose diet was carefully controlled a persistent and marked creatinuria was present even when a practically creatine-free diet was used.

2 Feeding gelatin as the principal source of protein did not affect the amount of creatine eliminated in the urine.

3 Calculated on the basis of the total amount of creatinine excreted, the coefficient for creatinine had a normal value, though the coefficient for preformed creatinine was very low.

4 The concentration of creatine and creatinine in the blood of this patient was entirely within the normal range. In fact chemical analysis of the blood revealed nothing unusual.

13 Powis F. and Raper H. S. *Biochem J* **10** 363 1916

14 Ziegler M. R. and Pearce N. O. *J Biol Chem* **42** 581 1920

15 Gibson R. B., and Martin F. T. *J Biol Chem* **49** 319 1921

5 A study of the excretion of uric acid and organic acid disclosed no significant facts

6 Administered creatine is quickly and quantitatively eliminated through the urine, about 84 per cent of the ingested creatine appearing unchanged and 16 per cent appearing as creatinine

7 The results of this experimental study indicate that the transformation of creatine to creatinine by the atrophied muscles is not affected, but that they are apparently unable to retain and synthesize creatine to phosphagen. The suggestion is made that the inability of the atrophied muscles to synthesize phosphagen, which was the most outstanding peculiarity of the metabolism of our patient, is associated with the more fundamental disturbance in the metabolism of glycogen of the muscles

TUBERCULOUS MENINGITIS WITH SYPHILITIC MENINGITIS TERMINATING IN RECOVERY

A REVIEW OF THE LITERATURE[†]

DAVID W KRAMER, M D

AND

B B STEIN, M D

PHILADELPHIA

Tuberculous meningitis has been looked on as a disease that must end disastrously. This fact, unfortunately, has been emphasized so frequently that when one mentions a case that terminated in recovery, not only is the diagnosis automatically challenged, but there is a tendency to discard all the positive observations and question the laboratory technic. However, a perusal of the literature on this subject will convince the most pronounced skeptic that there is no law in the science of medicine that disbars the meninges from localizing and overcoming an infection of the tubercle bacillus, and that some patients do recover from this disease. If tuberculosis of other tissues and organs may subside, then why not tuberculosis of the meninges? No doubt recoveries are rare, but the fact that some cases do terminate favorably should be recognized. Because of the rarity of this unexpected result, we are presenting the following case.

REPORT OF CASE

History—A colored man, aged 29, was admitted to the hospital on July 3, 1928, complaining bitterly of severe pains in the head. The family history was irrelevant. The patient had had gonorrhea in 1918 and a chancre in 1920. There was no history of pleurisy. The present illness dated back four days when the patient complained of a headache beginning in the frontal region, with sharp pains going around the head and down the neck. The frontal pain was sharp, shooting and continuous. Dizziness, ringing in the ears and diplopia were present at the onset. The patient was nauseated but did not vomit until the third day of his illness. He had been coughing for several months and occasionally had had blood-streaked sputum.

Examination—Examination revealed that the patient was fairly well nourished and well developed. The expression of the face was indicative of acute pain. The eyelids were tightly brought together to shut out the light. The pupils were irregular and reacted sluggishly to light, the right eye was turned inward, there was no ptosis of the lids. The neck was rigid, a few small glands were palpable. The heart sounds were regular but somewhat impaired, no murmurs were heard. Percus-

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* From the Medical Department, Jefferson Medical College, and the Medical Service of Dr S A Lowenberg, Philadelphia General Hospital

sion was impaired over the upper part of the chest on the right side, the breath sounds were harsher than normal and were bronchovesicular, a few scattered rales could be heard in this area. There was a generalized rigidity of the abdominal walls with a fairly marked hyperesthesia, the liver and spleen were not enlarged on percussion. Examination of the extremities showed that Kernig's and Brudzink's signs were positive on both sides, Babinski's sign could not be elicited. The spinal fluid was examined and about 50 cc was removed, there was apparently no increase in pressure, the fluid was cloudy, there were no organisms, the cell count was 1,200, 56 per cent being polymorphonuclears and 44 per cent lymphocytes. The blood count showed 4,900 leukocytes, 51 per cent polymorphonuclears, 44 per cent lymphocytes, 2 per cent eosinophils and 1 per cent basophils. The blood sugar was 75 mg per hundred cubic centimeters of blood, and the urea was 14 mg. The temperature was 100 F, the pulse rate, 96, and the respiratory rate, 32.

Treatment and Course—The following notes of the patient's progress were made.

July 6, 1928. The general condition was worse, the patient was irrational, the limbs were spastic. About 40 cc of a greenish-yellow spinal fluid was removed, under pressure, examination for evidences of tuberculosis gave negative results. The temperature was 99 F, the pulse rate, 90, and the respiratory rate, 30. The Wassermann reaction of the blood was 4 plus, with all antigens. A diagnosis of syphilitic meningitis was made.

July 7. Thirty grams (195 Gm) of sodium iodide was given intravenously. The spinal fluid had a cloudy yellowish appearance. The general condition of the patient was much improved.

July 8. The general condition was fair. Thirty grams of sodium iodide was given intravenously. A spinal tap was performed and 30 cc of spinal fluid removed under pressure.

July 10. The condition was gradually improving. The temperature was 98.4 F, the pulse rate, 92, and the respiratory rate, 24. Thirty grains of sodium iodide was given intravenously.

July 11, 12 and 13. The patient was given 10 cc of Pregl's iodine solution intravenously. The temperature, pulse and respirations were normal.

July 14, 15 and 16. The patient complained of headache, he did not feel well and seemed much weaker. The temperature was 101 F, the pulse rate, 100, and the respiratory rate, 30. On spinal tap, the fluid was clear. Examination of the spinal fluid at this stage showed a positive Levinson reaction and the formation of a pellicle. *Tubercle bacilli were found in the pellicle.* The use of iodides was discontinued.

July 17. The patient complained of intense headache, he was much weaker and was in a semistuporous condition. The temperature was 101 F, the pulse rate, 120, and the respiratory rate, 30.

July 20. The condition was much improved. The patient insisted on sitting up in bed. His appetite was good. The rigidity of the neck had subsided, but Kernig's sign was still present. Under slight pressure, spinal tap revealed a clear fluid, the cell count was 26, there was a faint trace of globulin. The temperature was 98.4 F, the pulse rate, 90, and the respiratory rate, 25.

Neurologic Consultation (report by Dr. B. Weiss). The pupils were irregular, they reacted sluggishly to light, there was palsy on both sides. The tongue protruded in the midline, there was no tremor. The lips puckered well. There was some rigidity of the neck. The power in the upper extremities was fair. There was no tremor of the extended hand. The reflexes of the biceps muscles were normal, those of the triceps muscles were diminished on the left. The abdominal

reflexes were normal. The knee jerks and the achilles tendon reflex were absent bilaterally. There was a positive bilateral Kernig sign. There was no clonus or Babinski sign. General slight hyperesthesia was present. Somnolence was also noted. The patient was mentally clear.

Observations of tubercle bacilli in the pellicle led to a diagnosis of tuberculous meningitis. The presence of greenish-yellow pus associated with an increase in polymorphonuclears in the spinal fluid suggested a superimposed purulent meningitis. A complete examination of the sinus and transillumination were advised to determine, if possible, the initial foci of infection.

The history of initial chancre with typical Argyll Robertson pupils and absent achilles tendon reflexes and knee jerks and the history of vesical disturbance and of sharp lancinating pains which the patient termed rheumatic, together with serologic observations, indicated a specific meningomyelitis with particular involvement of the posterior columns. The acuteness of the onset ruled out a purely tabetic involvement.

Ocular Examination (Dr O'Brien). The media were clear, the disks were oval. The edges were blurred, and the veins were overfull. There were no other pathologic conditions. The examination was made without mydriasis.

July 23. The patient had been doing fairly well. On that day he complained of severe pains in the left side of the neck. The temperature rose to 104 F, the pulse rate to 116 and the respiratory rate to 35. Examination revealed marked tenderness in the left side of the neck with swelling. Thirty cubic centimeters of clear spinal fluid was removed without pressure. Laboratory examination of the fluid gave negative results.

July 25. The spinal fluid showed a cell count of 105, with a faint trace of globulin, the Levinson reaction was positive. The temperature had subsided to normal and then rose to 101 F.

July 27. There was a sharp rise in temperature to 105 F, the pulse rate rose to 130 and the respiratory rate to 34. The patient was uncomfortable, he had difficulty in swallowing and complained of severe pains in the left side of the neck. Surgical consultation was requested. An examination was made by Dr Righter, who diagnosed the condition as acute cervical adenitis.

Thirty cubic centimeters of spinal fluid was removed under slight pressure. Laboratory examination gave negative results for tubercle bacilli and for the formation of a pellicle.

July 30. The condition had subsided completely. The temperature, the pulse rate and the respiratory rate were normal. The patient felt much better.

July 31. The general condition was good, the patient was improving and was able to sit in a chair. There was no complaint of pain. However, there was still a slight rigidity of the neck.

August 14. The patient was discharged apparently in good condition. The temperature, pulse rate and respiratory rate had been normal for three weeks. When he was discharged, a diagnosis of syphilitic and tuberculous meningitis was made.

October 7. The patient reported for observation, he was feeling well. He complained of some irritability of the bladder. The spinal fluid was examined, there were no cells and no increase in globulin. The Wassermann test gave negative results with both antigens. The colloidal gold curve was normal. The Levinson test, however, gave positive results.

Autopsy was performed on a guinea-pig that had been inoculated with the spinal fluid, the result was negative for tubercles. The autopsy was done approximately three months after the original inoculation.

The following year the patient felt well. An attempt was made to have him return to check up the studies of the spinal fluid, but he declined.

In the spring of 1930, an attempt was made to communicate with the patient for further observations. He had left town, but we were informed by a sister that he was living and feeling well.

Table 1 shows at a glance the observations on the spinal fluid.

TABLE 1—*Analyses of the Cerebrospinal Fluid*

Date, 1928	Appearance	Cell Count	Polymorpho nuclears	Lympho cytes	Globulin	Wassermann Reaction	Colloidal Gold Curve	Levinson Reaction	Pellicle	Tubercle Bacilli	Sugar, Mg
7/ 3	Cloudy	1,200	56	44	Heavy trace	+	1233342211				30
7/ 4	Cloudy, opalescent	500			Trace						
7/ 5	Cloudy	1,500	80	20	Trace			Nega tive			
7/ 6	Cloudy	3,750	93	7	Heavy trace	+++		Nega tive	Nega tive		
7/ 7	Yellowish, cloudy	1,303			Trace						
7/ 8	Cloudy	2,500	83	17		+	2333433222				
7/ 9	Slightly turbid	99			Trace						
7/10	Cloudy	82			Faint trace						
7/11	Slightly cloudy	283			Trace	Nega tive					37
7/12	Clear	250			Trace						
7/13	Clear	150		100	Trace	++					
7/14	Clear	250	19	75				Posi tive	Present	Present	
7/16	Clear							Posi tive	Present	Negative	
7/17	Clear					++			Present		
7/20	Clear	26			Faint trace				Present		
7/21	Clear	10			Faint trace	++++			None	None	
7/23	Clear	0			0						
7/24	Clear	0			0				Small	None	
7/25	Clear	105			Faint trace			Posi tive			
7/26	Clear	72			Faint trace				None		
7/27	Clear	7			Very faint trace				None	None	
7/30	Clear	6			Faint trace				None	None	
10/7	Clear	0			0	Nega tive	0000000000	Posi tive	None	None	

COMMENT

From the history and symptoms of the case, we were unquestionably dealing with some form of meningitis, the exact etiologic diagnosis demanding consideration. In the absence of micro-organisms, which

could not be demonstrated either by staining or by culture, that is, in the early course of the disease, we were inclined to consider it a meningitis other than the well recognized forms, such as meningococcic, pneumococcic or influenzal. The strongly positive Wassermann reactions in both the spinal fluid and the blood, the high cell count, the colloidal gold curve and the moderate range in temperature plus the negative observations already mentioned warrant a diagnosis of syphilitic meningitis. This diagnosis conforms with the symptoms and the laboratory studies usually found in syphilis of the central nervous system with meningeal involvement as mentioned by Stokes¹

The patient was treated accordingly with iodides both by mouth and intravenously and with mercurial inunctions. Spinal punctures were performed daily for relief from the symptoms and for observations on the course of the disease. The patient gradually improved during the first week, the temperature, pulse and respirations subsided and reached normal limits by the tenth day. Shortly afterward, however, there was a change in the patient's condition. He complained of intense headaches and marked weakness. There was a rise in temperature with a corresponding increase in the pulse and respiratory rates. The laboratory studies of the spinal fluid were as follows: the fluid was clear, the cell count was 250, the Levinson reaction was positive, formation of pellicle was present and on examination of this pellicle, tubercle bacilli were definitely found by Dr. Walter J. Crocker, chief clinical pathologist, who reported that "in three different fields, beaded acid-fast rod-shaped bacilli were found" which he believed were tubercle bacilli. The Ziehl-Neelsen acid-fast method was used in staining.

With these laboratory observations, a diagnosis of tuberculous meningitis was made, and the usual unfavorable prognosis was given. The patient was uncomfortable for several days. Subsequently, however, there was an unexpected improvement and a decided change in the spinal fluid. Within six or seven days, he had recovered sufficiently to insist on sitting in a chair. The rigidity of the muscles in the back of the neck had subsided but Kernig's sign was still present. Except for an attack of acute cervical adenitis, he made an uneventful recovery, and he was discharged from the hospital six weeks after his admission. The final diagnosis was syphilitic meningitis with tuberculous meningitis terminating in recovery.

Assuming that the diagnosis is correct, the next question to decide is what constitutes an authentic case and how does this case measure up with the required specifications. Whether or not we are justified in labeling this case tuberculous meningitis entails some discussion.

¹ Stokes, John H. *Modern Clinical Syphilology*, Philadelphia, W. B. Saunders Company, 1926, p. 925.

This question has been thoroughly discussed in various contributions on the subject by Martin,² Pitfield,³ Cramer and Bickel,⁴ Borruso⁵ and others. The consensus indicates that the significant and convincing observations are (1) the formation of a pellicle with the demonstration of tubercle bacilli in the fluid, (2) postmortem examination showing evidences of an old meningitis which has healed, (3) inoculation of the spinal fluid into a guinea-pig, followed by the development of tuberculosis. Other collateral observations that may assist in arriving at a diagnosis of tuberculous meningitis are cytodiagnosis of the fluid, lymphocytosis usually being present, one must not forget, however, that there may be exceptions to this rule, as polymorphonuclearcytosis is found occasionally, tubercles in the choroid, evidences of tuberculosis elsewhere in the body, the Levinson test of the spinal fluid, reduction of chlorides, and the tuberculin test.

It would be unreasonable to expect all of the aforementioned requirements to be present in every case. The demonstration of tubercle bacilli in the spinal fluid has been accepted as fairly conclusive evidence of a positive diagnosis of tuberculous meningitis. In our case, these organisms were definitely found, the formation of pellicle was noticed on several occasions, the Levinson reaction was positive, there was suggestive evidence of involvement of the lungs, and cervical adenitis was present. All of these symptoms seem to warrant a diagnosis of tuberculous meningitis. The fact that the organisms were found only once may cast some doubt on the diagnosis. Some authorities on tuberculosis, particularly when dealing with the pulmonary form, insist on more than a single report confirming the presence of tubercle bacilli, realizing as they do, that in the examination of specimens of sputums an error may be made in the laboratory. However, the examination of spinal fluids requires more skill and care. As a rule, in laboratories such examinations are performed only by those who are well trained for this type of work. In our case, the positive observation of the tubercle bacilli was confirmed by the chief of the laboratory and others who were present. The presence of the organisms in the spinal fluid was unquestionably established. The failure to demonstrate the bacilli in other specimens of spinal fluid from this case may or may not be significant. We do not know exactly how the micro-

2 Martin, Alfred E. The Occurrence of Remissions and Recovery in Tuberculous Meningitis, A Critical Review, *Brain* **32** 209, 1909

3 Pitfield, R. I. Recovery from Tubercular Meningitis, with Report of Cases, *Am J M Sc* **146** 37, 1913

4 Cramer, A., and Bickel, G. La méningite tuberculeuse, est-elle curable? *Ann de méd* **12** 226, 1922

5 Borruso, G. Curability of Tuberculous Meningitis, *Policlinico (sez med)* **36** 493, 1929

organisms get into the spinal fluid, nor do we understand whether or not this is a daily performance. Is it not likely that only on certain occasions the tubercle bacilli work their way through the lymphatic glands and get into the cerebrospinal fluid, and that if one happens to obtain the spinal fluid on that particular day and has the studies made by a trained examiner one will obtain a positive report? On the other hand, it is not unusual to obtain negative reports on the spinal fluid in cases in which inoculation into guinea-pigs produced tuberculosis, and it is not unusual to have negative spinal fluids in cases in which the diagnosis is proved by autopsy. Another explanation for this discrepancy, if we may call it such, is the fact that only a limited number of the bacilli were free in the circulation and the spinal fluid. This fact likewise enters in the possible explanation for the recovery in these cases and is discussed under that heading. The weak link in the chain was the failure to produce tuberculosis on inoculation of the spinal fluid into a guinea-pig after a period of three months. This negative observation, however, does not seem significant enough to nullify the positive evidence because it is possible that the tubercle bacilli were not present in sufficient number to infect the animal. Sometimes the animal is killed before the disease has time to develop. Bezançon and Gastinet⁶ and Tilli⁷ reported inoculations of guinea-pigs requiring fourteen and thirty months, respectively, before the disease appeared in the animals, they suggested that the possible explanation was a diminished virulence of the organisms.

An interesting angle to the discussion of the diagnosis in this case is the question of syphilis. Were we dealing with a bona fide case of syphilitic meningitis in the beginning, which later proved to be fertile soil for a temporary involvement of tubercle bacilli or was it primarily a case of tuberculous meningitis with positive serologic reactions, as reported recently by Schaffle and Riesenbergs⁸? In their contribution they found that occasionally the spinal fluid may show a strongly positive Wassermann reaction in nonsyphilitic meningitis. Their series consisted of 8 cases, 5 of which were tuberculous meningitis. The Wassermann reaction of the blood was negative in each case. However, the possibility of the development of tuberculous meningitis in a syphilitic person must be borne in mind. Despite the fact that other forms of tuberculosis are prone to develop in syphilitic persons, the combination of syphilis and tuberculous meningitis is strikingly infre-

6 Bezançon and Gastinet, quoted by Cramer and Bickel, p 238 (footnote 4)

7 Tilli, P. Meningite tubercolare, tentativi di cura con Reiniezioni sottocute del liquido cefalo-rachidiano del paziente, Polichinico (sez prat) **23** 1357, 1916

8 Schaffle, K, and Riesenbergs, M. The Occurrence of Positive Wassermann Reactions in the Spinal Fluid of Tuberculous and Other Nonsyphilitic Cases of Meningitis, Am J M Sc **178** 632, 1929

quent in the literature Pillotti⁹ reported 1 case of tuberculous meningitis in a syphilitic patient who had had antisyphilitic treatment Mallardi¹⁰ presented a case with this combination, in which, judging from laboratory and clinical observations, it was difficult to decide exactly whether the child had a tuberculous or a syphilitic meningitis

In our case, although tuberculosis of the meninges may have existed from the beginning, the evidence suggesting the presence of syphilitic meningitis at the onset is too strong to overlook The fact that the patient improved under antisyphilitic treatment may also suggest the diagnosis of syphilitic involvement It is possible and it is our belief that the iodides, which were given both intravenously and by mouth, may have been instrumental in the breaking down of a healed tuberculous focus either in the lungs or more likely in a lymph node The tubercle bacilli thereby set free settled down on the already weakened meninges and this resulted in a more or less localized meningitis The fact that the patient recovered need not exclude the diagnosis of tuberculous meningitis

CURABILITY OF TUBERCULOUS MENINGITIS

There have been many contributions in the literature pertaining to the curability of tuberculous meningitis Rillet is credited with the first discussion in 1853 The number of patients reported as cured would probably mount to 400 or more Cramer and Bickel collected 250 cases, others have similarly collected groups of reported cures, but when these reports are carefully scrutinized, the number of acceptable authentic cases is considerably less Of the 250 cases collected by Cramer and Bickel, they considered only 46 as authentic, Martin, in 1909, collected 20 cases, Pitfield, in 1913, in his contribution raised the number to 29 cases, Harbitz,¹¹ in 1921, and Borrusso, in 1929, also gathered case reports in their discussions on the curability of tuberculous meningitis

We have attempted to compile a complete list of the reported cures and have arranged them in tabular form In this way, repetition and unintentional exaggeration of the figures were obviated In selecting authentic cases, the qualifications already mentioned in the discussion of the diagnosis of our case were adhered to We included Schaeffer's¹²

9 Pillotti, quoted by Schaffle and Riesenbergl Am J M Sc **178** 633, 1929

10 Mallardi, M Un caso di meningite sifilitica in soggetto tubercolotico, *Pediatria* **28** 1138, 1920

11 Harbitz, F The Curability of Tuberculous Meningitis, Am J M Sc **161** 212, 1921

12 Schaeffer, S Tuberculous Meningitis Report of a Case in an Adult with Recovery, New York M J **48** 77, 1913

case because of the positive results after inoculation into a guinea-pig. Additional cases recently reported are those of Gehrke,¹³ Vialard and Darleguy,¹⁴ Vedel, Giraud and Puesch,¹⁵ McMahon,¹⁶ Neidhardt,¹⁷ Oppenheim,¹⁸ Wiese,¹⁹ Dima²⁰ and Jousset and Perisson.²¹ These cases, together with ours, raised the number to 73. Reports of cures without sufficient scientific proof of the diagnosis were discarded.

It may be pertinent to take up the question as to what constitutes a cure. Some patients who were reported as cured had recurrences of meningitis, and in isolated cases the recurrences were fatal. This question cannot be settled definitely as there are no iron-clad rules to follow in deciding the point. An arbitrary period of freedom from symptoms and subsidence of the infection may be designated. Since tuberculous meningitis is considered a fatal disease, may it not be assumed that if the patient has recovered from the symptoms and signs sufficiently to get about, leave the hospital and remain free from the symptoms for from six to twelve months, his case may be classified as a "cure." A "cure" in a case of tuberculous meningitis should really be interpreted as a clinical recovery through which the patient has escaped an apparently inevitable doom that awaits sufferers of this disease. The patients who have recovered may show some after-effects or sequelae in various forms. However, the fact remains that the patients did not die, and hence they are referred to as being "cured" or having "recovered."

Table 2 shows the statistical data of the cases reported as cures and the authors who quoted them.

13 Gehrke, A. Kann die Meningitis tuberculosa Heilen? Beitr z Klin d Tuberk **61** 310, 1925.

14 Vialard and Darleguy. Recovery from Tuberculous Meningitis, Bull et mem Soc med d hôp de Paris **49** 522, 1925.

15 Vedel, Giraud, and Puesch. Acute Tuberculous Meningitis, Bacteriologically Confirmed, Rapid Recovery Persisting for Thirty-Two Months, Bull et mem Soc med d hôp de Paris **50** 388, 1926.

16 McMahon, B. T. Recovery from Tuberculous Meningitis, Am Rev Tuberc **13** 216, 1926.

17 Neidhardt, K. Recovery of Case of Tuberculous Meningitis After Intra-Lumbar Treatment with Tuberculin, Munchen med Wchnschr **73** 823, 1926.

18 Oppenheim, E. A. Tuberculous Meningitis Cured by Freedman Vaccination, Ztschr f Tuberk **45** 316, 1926.

19 Wiese, O. Recovery from Tuberculous Meningitis, Munchen med Wchnschr **73** 1937, 1926.

20 Dima, F. Apparent Cure of Tuberculous Meningitis and Recurrence, Riforma med **45** 990, 1929.

21 Jousset, A., and Perisson, J. Cure of Tuberculous Meningitis or Remission in Three Cases Treated with Allergine (Tuberculous Vaccine), Bull et mém Soc méd d hôp de Paris **53** 654, 1929, Rev internat de med et de chir **40** 75, 1929.

It is almost impossible to collect all of the cases of tuberculous meningitis terminating favorably. No one can say how many cases were rejected because of insufficient scientific data, e g, Browning's²² 4 cases and others, may actually have been infections due to the tubercle bacillus. This applies to patients in whose cases the clinical evidence pointed to tuberculous meningitis but in which proper laboratory studies were not carried out. In the cases reported by Hamill²³ and the one quoted by Abt,²⁴ the diagnosis was acceptable, but the reports were never included in the literature because of the aforementioned reasons. On the other hand, there may have been genuine cases of tuberculous meningitis terminating in recovery, but on account of the rarity of the condition the physicians hesitated to diagnose them as such and considered Koch's infection as the etiologic factor. However, even with the limited number of cases available, one must admit that some cases may be exceptions to the general rule and that patients do recover from this disease.

An analysis of the 73 cases reveals the following statistics as to sex, age and laboratory observations

		Number of Cases	Percentage
Males		40	55
Females		23	31
No mention of sex		10	

Age, Years	Cramer and Bickel's List of 46 Cases		Author's List of 73 Cases, Including Cramer and Bickel's	
	Number of Cases	Percentage	Number of Cases	Percentage
Up to 2½	1	2.5	1	1.4
2½ to 5	6	15.0	14	19.2
6 to 10	10	25.0	12	16.4
11 to 20	11	27.5	14	19.2
Above 20	12	30.0	24	33.0
Not mentioned	6		8	

SIGNIFICANCE OF LABORATORY STUDIES

The tubercle bacillus was present in the spinal fluid in 47 cases (64 per cent), it was not found in 16 cases (22 per cent), and it was not mentioned in 10. When the spinal fluid was inoculated into a guinea-pig, tuberculosis resulted in 30 instances (41 per cent), the inoculation was negative in 4 cases (6 per cent) and was either not done or at least not mentioned in 39 cases (53 per cent). This procedure evidently has been neglected in many cases, and in view of the importance of definitely establishing a diagnosis, it may be worth while to emphasize that nothing should be omitted when laboratory studies are

22 Browning, C. C. Report of Four Cases of What Appeared to Be Tuberculous Meningitis with Apparent Permanent Arrestment, *Med Rec* 86 325, 1914

23 Hamill. Tr Am Pediat Soc, *Arch Pediat* 27 697, 1910

24 Abt. Tr Am Pediat Soc, *Arch Pediat* 27 698, 1910

TABLE 2—Analysis of Authentic Cases of Tuberculous Meningitis Terminating in Recovery

Report of Case	Quoted by	Sex	Age, Years	Duration of Illness	Site of Tubercle Bacilli	Tubercle Bacilli in Choroid	Tubercle Bacilli in Spinal Fluid	Guinea Pig Inoculation	Cytodiagnosis	Autopsy	Comment
1 Rillet	1853 Harbitz		5½	3 months							
2 von Bokai	1862 Harbitz	F	4		Lung					Confirmed	
3 von Leube	1889 Harbitz	M	12				Positive			Confirmed	Well 5 months later
4 Barth	1894 Harbitz	M	20	3 months						Confirmed	
5 Freyhan	1891 Cramer and Bickel	M	19	6 weeks	Lung		Positive			Confirmed	Died 3 years later of tuberculosis of lung
6 Janssen	1896 Harbitz	M	37	8 months			Positive				Complete cure
7 Busse	1900 Harbitz	F	10				Positive				
8 Henkel	Cramer and Bickel	M	8	9 months	Lung				Lymphocy tosis	Confirmed	Recurrence 22 months later
9 Rocaz	1901 Martin	M	2½	6 months			Positive				Complete cure
10 Barth	1902 Cramer and Bickel	F	17	Short	Glands and lungs (?)		Positive		Polymorpho nuclear lymphocy tosis		Well 3 months later
11 Gross	1902 Cramer and Bickel	F	5	Short			Negative	Positive	Lymphocy tosis		Complete recovery
12 Alanzano	1903 Cramer and Bickel	M	7		Glands		Negative	Positive	Lymphocy tosis		
13 Rossini	1905 Martin	M	6½	2 months	Glands		Positive	Positive	Lymphocy tosis		
14 Carriere and L'Hôte	1905 Cramer and Bickel	M	4			Positive	Negative	Positive	Lymphocy tosis		
15 Carriere and L'Hôte	1905 Cramer and Bickel	F	33	5 weeks		Positive	Negative	Positive	Lymphocy tosis	Confirmed	Recurrence 3 months later, fatal recurrence in 4 years
16 Carriere and L'Hôte	1905 Cramer and Bickel	M	30	3 months			Positive	Positive	Lymphocy tosis		Complete cure
17 Carriere and L'Hôte	1905 Cramer and Bickel	M	25	5 weeks			Negative	Positive	Lymphocy tosis		
18 Sicaud	1905 Cramer and Bickel	F	14				Negative	Positive	Lymphocy tosis		Well 7 months later
19 Glasse and Abrami	1905 Cramer and Bickel	F	6	2 months			Positive	Positive	Lymphocy tosis		Well 6 months later
20 Vaquez and Digne	1905 Cramer and Bickel	F	5	5 weeks			Negative	Positive	Lymphocy tosis		
21 Todeshi	1905 Cramer and Bickel	F	3½	Slow cure			Negative	Positive	Lymphocy tosis		Well 7 months later
22 Riebold	1906 Cramer and Bickel	F	9	Extremely slow, 3 months	Glands		Positive	Positive	Lymphocy tosis	Confirmed	Confirmed after 3 years
23 Hutinel and Tisser	1907 Cramer and Bickel	M					Negative	Positive	Lymphocy tosis	8 years, confirmed	
24 Jemma	1907 Cramer and Bickel	M					Positive	Positive	Lymphocy tosis		
25 Rumpel	1907 Cramer and Bickel	M			Lungs 4 years later		Positive	Positive	Lymphocy tosis		

26	Garcso	1908	Cramer and Bickel	M	8		Negative	Positive	Lymphocytosis	Complete cure 2 years later Complete cure
27	Stark	1908	Cramer and Bickel	M	44		Positive			
28	Stiles	1908	Cramer and Bickel				Positive			
29	Stiles	1908	Cramer and Bickel				Positive			Cure with right hemiplegia
30	Dunn	1910	Dunn	F	3	3 weeks	Positive			
31	Warrington	1910	Cramer and Bickel	M	11	Slow cure, several months	Positive			
32	Castaigne and Goulaud	1911	Cramer and Bickel	M	20		Positive	Positive		Cure confirmed 1 year later
33	Aviragnet and Fivier	1911	Cramer and Bickel	M	5	5 weeks	Negative	Positive		Well 7 months later
34	Archangelsky	1911	Cramer and Bickel	F	8		Positive	Negative		Well 2 years later
35	Wannetschek	1911	Cramer and Bickel	M	4	6 weeks	Positive			
36	Hoekstetter	1912	Cramer and Bickel	M	21	Slow cure, 6 months	Positive	Negative		
37	Barbier and Gougelet	1912	Cramer and Bickel	M	5		Negative	Positive		Well 1 year, fatal recurrence
38	Me Cotin	1912	Cramer and Bickel	M	21	2 1/2 months	Positive	Positive		Well 8 months later
39	Brooks, Tyrrel and Gibson	1912	Cramer and Bickel	F	4		Positive		Confirmed	Died several years later of tuberculosis
40	Schaeffer	1913	Kramer and Stein	M	39	2 3 weeks	Negative	Positive	Polymorphonuclears	Complete cure
41	Rehman and Raneh	1913	Cramer and Bickel	F	21		Positive	Negative		Complete cure
42	Bezaneon and Gastonel	1913	Cramer and Bickel			2 months	Negative	Positive		Well 2 years later
43	Pittfield	1913	Cramer and Bickel	M	55	3 weeks	Positive			
44	Estramann	1914	Harbitz	M	37	1 year	Positive		Confirmed	
45	Rosle	1914	Harbitz	F	37	17 months	Negative		Confirmed	
46	Bokay	1914	Cramer and Bickel	M	14		Negative	Positive		Well 1 year later
47	Bokay	1914	Cramer and Bickel	M	12		Positive	Positive		Well 2 1/2 years later
48	Fonzo	1915	Cramer and Bickel		11		Positive			Complete cure
49	Bacigalupo	1915	Cramer and Bickel			20 days	Positive			Complete cure
50	Bacigalupo	1915	Cramer and Bickel			20 days	Positive			Complete cure
51	Tilli	1916	Cramer and Bickel	F	7 mo	2 months	Positive	Positive 30 months later		Fatal recurrence 6 months later

TABLE 2—Analysis of Authentic Cases of Tuberculous Meningitis Terminating in Recovery—Continued

Report of Case	Quoted by	Sex	Age, Years	Duration of Illness	Site of Tubercle Bacilli	Tubercle Bacilli in Choroid	Tubercle Bacilli in Spinal Fluid	Guinea Pig Inoculation	Cytodiagnosis	Autopsy	Comment
52 Tuli	1916 Kramer and Bickel	M	8				Positive				Reappearance in 2 months, cure with sequelae
53 Grote	1917 Kramer and Bickel	F	27	2 months			Positive				
54 Grote	1917 Kramer and Bickel	F	12	1 month			Positive				
55 Van den Boert	1918 Kramer and Bickel	F	3½	6 months			Negative	Positive			
56 Harbitz	1919 Harbitz	M	32				Positive				
57 Harbitz	1919 Harbitz	M	30	4 months			Positive, after death				
58 DeMassury	1920 Kramer and Bickel	F	23		Pulmonary infection suspected Tubroid		Positive				Complete cure
59 Barber and L'Echelle	1920 Kramer and Bickel	F	37	Chronic course			Positive				Complete cure
60 Kramer and Bickel		M	19	6 months			Negative	Positive			Complete cure 18 months later Hemiplegia
61 Gehrecke	1925 Kramer and Stein	F	53	7 months	Lungs		Positive	Positive			Well 6 months later
62 Vialard and Darleguy	1925 Kramer and Stein	M	22	5 months	Lungs (?)		Positive	Positive	Lymphocytosis		Well 32 months later
63 Vedel, Giraud and Puseh	1926 Kramer and Stein	F	23	1 week			Positive	Positive	Lymphocytosis		Well 10 months later
64 McMahon	1926 Kramer and Stein	F	28	1 year	Lungs		Positive	Positive	Lymphocytosis		Well 10 months later
65 Neidhardt	1926 Kramer and Stein	M	12	3 weeks			Positive				Well some months later Recovery
66 Oppenheim	1926 Kramer and Stein	M	10	14 days	Lungs		Positive		Lymphocytosis		Reappearance
67 Wiese	1926 Kramer and Stein	M	10	5 months			Positive		Lymphocytosis		Recovery
68 Dima	1929 Kramer and Stein	M	4	7 weeks			Positive		Lymphocytosis		Well 6 months later
69 Borruso	1929 Kramer and Stein	M	½	12 days	Knee (5 mm ulcer)		Positive	Positive	Lymphocytosis		100 months later, final recovery
70 Jousset and Perisson	1929 Kramer and Stein	F	11	6 months			Positive		Lymphocytosis		Apparently well 7 months later
71 Jousset and Perisson	1929 Kramer and Stein	F	18	2 months			Positive		Polymorpho-nuclears		Well 2 years later
72 Jousset and Perisson	1929 Kramer and Stein	M	36	2 months			Positive		Lymphocytosis		
73 Kramer and Stein		M	29	10 days	Lungs glands		Positive	Negative	Lymphocytosis		

carried out in suspected cases of meningitis. In 15 cases in which the tubercle bacilli could not be demonstrated in the spinal fluid, the diagnosis was established by positive inoculation into guinea-pigs. This fact is important because in some cases the organisms are so few as to make it exceedingly difficult to demonstrate their presence under the microscope. The doubly positive observation in which tubercle bacilli were present in the spinal fluid with positive inoculation into a guinea-pig was found in only 10 cases (13.7 per cent) of the series.

Cytodiagnosis was mentioned in 24 of the cases. Lymphocytosis was the usual observation, however, on three occasions polymorphonuclears predominated.

Tuberculous lesions elsewhere in the body may be of interest when discussing the possible explanations for recovery in tuberculous meningitis. This condition was present in twenty-six patients (35.6 per cent). The most common site was in the lungs and the pleura (18 cases), the lymph glands were next (7 cases), and there was one instance each of infection in the abdomen, the knee and the skin.

EXPLANATION OF RECOVERY IN TUBERCULOUS MENINGITIS

The possible reasons for favorable termination of this most dreaded disease may be grouped under three headings: (a) clinical, (b) bacteriologic and (c) pathologic. Under the first group, age is important. A glance at the tabulation containing the incidence according to age shows that up to 2½ years only one patient recovered. Except for the discrepancy in the period from 2½ to 5 years, one could well infer that the older the patient, the better his chances for escaping the almost inevitable fatal termination. This deduction was well demonstrated in Cramer and Bickel's table. No doubt, advancing age does give the person more powers of resistance. One need merely mention the unusually high mortality rate for tuberculous meningitis in infants. The disease is invariably fatal up to 2 years. Besides the natural resistance that develops with years, it is also possible that the tissues gradually learn to cope with the tubercle bacilli. This has been mentioned by some authors who look on healed lesions in the lungs or old glandular infections as having the same beneficial effect as a vaccine would have. It is possible that the tissues may develop some immunologic properties that enable the person to limit the infection and ultimately to control it.

Bacteriologic influences depend on the number of organisms, their virulence and also the strain. It is possible that the favorable termination in some of the cases may have been due to the small numbers of tubercle bacilli distributed throughout the body. This fact was also mentioned in the discussion of the unsuccessful inoculation of tubercle bacilli into guinea-pigs. Virulence of the organism and its rôle in infec-

tion are too well known. Discussion on this phase seems unnecessary. Another point of interest may be the influence of the type of organism or strain of tubercle bacilli on recovery. Cramer and Bickel²⁵ and Landouzy and Gougerot²⁶ discussed what may be considered a peculiar form of reaction of the tissues to the infection. They emphasized the fact that the usual tendency for the formation of tubercles was lacking in these cases. Pathologic reports on the appearance of these cases, which were studied at later times, mentioned the fact that the meninges were congested and infiltrated, with thickening. There may be abundant exudate, but no tubercles in the subarachnoid space. The tendency to fibrosis is apparent. The brain is only slightly involved. There is a lessened tendency to overdistention of the ventricles with fluid. This may be due to a diminished inflammatory reaction of the meninges and the brain. Microscopically, intense congestion of the meninges with infiltration was noted, there was no nodular formation, many bacilli were found in the sections and many in the fluid. The presence of tuberculous meningitis as part of a generalized tuberculosis is a hopeless situation.

PROGNOSIS

The outlook for the patients who have survived is uncertain. Many cases have been observed for three years without a recurrence. However, some of them subsequently have reinfections, either in the form of a meningitis or the breaking down of another focus, which may terminate fatally. Some of the cases have sequelae in the form of deafness, monoplegia, blindness or persistent headaches.

We doubt whether much can be learned from a study of these cases with the hope of improving our therapeutics. Some physicians have been enthusiastic concerning their particular form of treatment, which varies from tuberculin therapy to surgical intervention. Decompression has been attempted, repeated lumbar punctures have been endorsed by some, autoserotherapy by reinoculation of the spinal fluid has been advised, and injections of tuberculin, both under the skin and into the dura, have been tried. It is questionable whether any form of treatment can be proved to be a determining factor in the recovery. It is possible that repeated spinal punctures may help to give relief and may spare some damage to the cerebral tissue from overdistention of the ventricles. It is likely that when a patient does recover the main factors are the individual resistance and a lowered virulence of the infecting agent.

The prognosis of tuberculous meningitis is still extremely doubtful. One cannot tell offhand which patients have a chance for recovery, but

25 Cramer and Bickel, p. 239 (footnote 4)

26 Landouzy and Gougerot, quoted by Borrusso, p. 499 (footnote 5)

we agree with Dunn ²⁷ that the family may be encouraged with the fact that there is a possible chance for a favorable termination, however remote that chance may be. No rules can be formulated with the type of onset as a guide because among the recoveries reported, some cases appeared with explosive symptoms while others began with a mild onset. The older the patient, the greater is the resistance and the better is the chance for a favorable result.

SUMMARY AND CONCLUSIONS

The report of a case in a Negro with evidences of syphilitic meningitis has been given, subsequent observations of tuberculous meningitis were made, and a favorable termination reported. A review of the literature reveals a number of contributions on the curability of tuberculous meningitis and numerous reports of cures. This number has been considerably reduced because of insufficient scientific data.

Seventy-three cases of presumably authentic cures were collected. A study of this group of cases does not enlighten us with information that may be of value in the direct treatment for this disease in the future.

Cures have been attributed to various factors such as the age and the resistance of the patient and a low virulence of the organism. Statistics of the collected cases show the highest percentage of cures among patients above 20 years of age (33 per cent) and the lowest percentage in infants.

The traditional and fixed idea that a patient with tuberculous meningitis must die should be reconsidered. No doubt, a recovery is extremely rare, but no one can foretell when this unexpected favorable termination may occur. The tendency to discard the diagnosis of tuberculous meningitis and disregard such laboratory observations as the presence of tubercle bacilli and successful inoculation into guinea-pigs, merely because the patient recovered, seems unscientific and illogical.

Dr. Walter J. Crocker and the laboratory staff gave excellent cooperation in managing the scientific studies in this case.

²⁷ Dunn, C. H. The Cytodiagnosis of Tuberculous Meningitis and the Possibility of Recovery, *Arch. Pediat.* **27**: 685, 1910.

THE CAUSE OF EXOPHTHALMIC GOITER

A BIOCHEMICAL HYPOTHESIS *

WILLIAM S REVENO, M D

DETROIT

It is quite generally agreed, although with some dissatisfaction, that the thyroid gland is responsible, when abnormally active, for the symptoms that characterize exophthalmic goiter. A vast literature has accumulated on this subject, with the majority of writers and investigators favoring the thyrogenic origin of the disease. A few have taken exception to this view, the most notable among these being McCarrison, who for many years has stoutly maintained that the disease is of toxic origin, and that the toxin or toxins originate in the intestinal tract. Plummer,¹ who favors the thyrogenic theory, described the disease as one in which the symptoms are due to dysfunction of the thyroid, excess thyroxine as well as an abnormal substance being present. McCarrison,² however, stated that "in the vast majority of cases the excitation which determines the gland's derangement is toxic, and is one which initiates disturbances of the whole endocrine system." There is an obvious difference of opinion in these two views, a difference that will not be adjusted until a more accurate knowledge is had of all of the disturbing substances other than thyroxine whether they originate in the thyroid or elsewhere. The view held by McCarrison seems to have the advantage in that it is arrived at by a consideration of the rôle played by three factors, nutritional, psychic and toxic. By his extensive studies of the changes produced in the thyroid gland in disturbances of nutrition and in toxic states, McCarrison established a strong support for his attitude. He showed in a convincing manner that changes that tend to destroy functioning thyroid tissue and ultimately to produce a condition of hypofunction may be induced by the toxins resulting from the feeding of infected material, also³ that the ingestion of amino-acids has an effect on the thyroids of tadpoles—a reduction in the size and number of the vesicles, and a decrease in the weight and length of the gland resulting. Tyrosine is the only one of the amino-acids that sometimes causes congestive and degenerative changes. McCarrison investigated also the effects of ingestion of histamine and tyramine on pigeons and rats⁴ and found a tendency for a reduction in

* Submitted for publication, Jan 2, 1931

1 Plummer, H S, quoted by Kendall, E C. Thyroxine, Am Chem Soc Monog Ser No 47, New York The Chemical Catalog Company, 1929

2 McCarrison, R. The Thyroid Gland, New York, William Wood & Company 1917

3 McCarrison, R. Indian J M Research **11** 1136, 1924

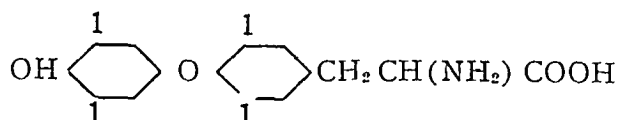
4 McCarrison, R. Indian J M Research **11** 1154, 1924

the size of the thyroid by both amines. He expressed the opinion that the ingestion of tyramine may possibly cause exophthalmos although this result may be rare. This evidence, while it may not be altogether convincing, serves a purpose in pointing an accusing finger at the intestinal tract as the source for the substances that are responsible for the disturbance known as exophthalmic goiter.

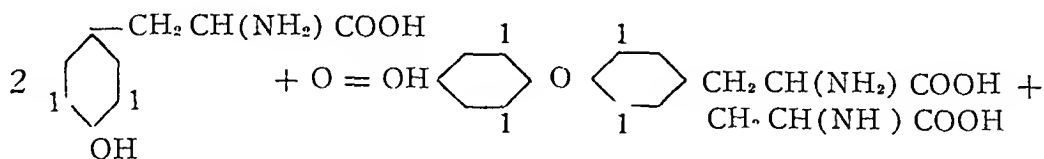
The symptoms in exophthalmic goiter may be adequately divided into those that are produced by thyroxine and those produced by a substance resembling epinephrine. From the present knowledge of the pharmacologic action of thyroxine, such symptoms as loss of weight, gastro-enteritis, diarrhea and tachycardia proportionate to the increase in metabolism may be readily explained. The symptoms attributable to the epinephrine-like substance do not, however, conform to the recognized major pharmacologic effects of epinephrine and it is necessary, therefore, to look to other substances, closely related to epinephrine, as being responsible for the extreme irritability of the vegetative nervous system, the tremor, elevated blood pressure and exophthalmos.

CHEMICAL COMPOSITION OF THYROXINE, EPINEPHRINE AND TYRAMINE

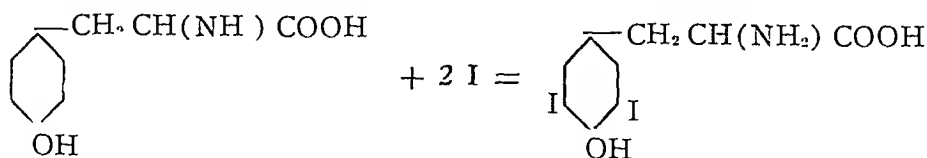
There is a most interesting connection between the chemical constitution of thyroxine and epinephrine. Thyroxine was isolated originally by Kendall in 1915,⁵ and the chemical formula was determined as



by Harington and Barger,⁶ who showed conclusively that it resulted from the oxidation of two molecules of 3,5 diiodotyrosine in this manner



The 3,5 diiodotyrosine, which is the precursory substance of thyroxine, is derived from the amino-acid tyrosine by the addition of two atoms of iodine in the 3 and 5 positions in the benzene ring



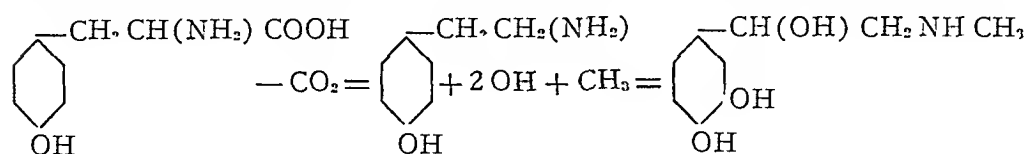
5 Kendall, E. C. The Isolation in Crystalline Form of the Compound Containing Iodin, Which Occurs in the Thyroid, *J. A. M. A.* **64** 2042 (June 19) 1915

6 Harington, C. R., and Barger, G. *Biochem. J.* **21** 169, 1927

According to Oswald,⁷ diiodotyrosine may in turn be deiodized by tyrosine in the alimentary canal

The amino-acid tyrosine normally produced in the intestinal tract as an end-product of the digestion of protein is therefore the parent substance of thyroxine, 3,5 diiodotyrosine is also produced in the intestine since it has never been isolated in crystalline form from the thyroid gland (although it may be present there)⁸ and, too, with both iodine and tyrosine present in the same region, it is fair to assume that synthesis of diiodotyrosine may logically take place there

Epinephrine is 1,2 hydroxyphenyl, 4 hydroxyethylmethylamine, and is derived from tyrosine first by splitting off CO₂, forming hydroxyphenylethylamine, and then by oxidation and methylation to epinephrine



It is probably produced in the intestine, and its content in excised suprarenal glands may be increased by incubation with tyrosine⁹

There is a common source in tyrosine for both thyroxine and epinephrine, and the suggestion occurs at this point that disturbances in the normal metabolism of this amino-acid may constitute the underlying factor in exophthalmic goiter

As far as is known, tyrosine is utilized for the production of two very important substances, thyroxine and epinephrine. Any excess probably undergoes decomposition by intestinal bacteria to phenol, p-cresol and p-hydroxyphenylacetic acid (by decarboxylation), and to tyramine. These substances are probably detoxicated by the liver, the phenols being eliminated as ethereal sulphates, and the tyramine as p-hydroxyphenylacetic acid¹⁰. Certain conditions may, however, interfere with this orderly procedure, and the overproduction of tyramine a base in which the action resembles that of epinephrine in many respects, may result

CHANGES IN THE NORMAL TYROSINE-TYROSINASE REACTION

The first of these conditions is an alteration in the reaction between tyrosine and the ferment tyrosinase whereby the pigment melanin results. Under normal conditions this reaction proceeds in the follow-

⁷ Oswald Ztschr f physiol Chem 62 432, 1909

⁸ Kendall, E. C. Thyroxine, Am Chem Soc Monog Ser No 47, New York, The Chemical Catalog Company 1929

⁹ Halle, W. L. Beitr z chem Phys u Path 8 276, 1906

¹⁰ Stewart, F. H. J Ment Sc 75 53, 1929

ing manner ¹¹ Tyrosine and tyrosinase together form red pigment (This is the pigment responsible for the red discoloration that appears on the cut surface of raw potato when exposed to the air) After several hours, this red substance becomes colorless, this phase of the reaction is accomplished best in a vacuum or in the presence of an inert gas in a medium ranging between p_{H_6} and p_{H_8} . Finally, this colorless substance is converted to melanin in the presence of oxygen Presumably, under altered conditions, such as an excess of tyrosine or a lack of tyrosinase or a change in the hydrogen ion concentration or the gaseous tension of the medium, the normal reaction does not take place and the base tyramine may be produced

The most important factor in the production of tyramine is that which is responsible for interference with the normal decomposition of tyrosine by bacteria The production of tyramine from tyrosine is assumed to take place in the same manner and under the same conditions as the production of histamine from histidine Folin and Denis ¹² found that certain *B. coli* in alkaline intestinal mediums promote the destruction of tyrosine by decarboxylation and the production of phenols which are detoxified by the liver and eliminated by the kidney These same bacilli will, in an acid medium, produce the base tyramine Hanke and Koessler ¹³ found in a large series of experiments that the amines (tyramine and histamine) were not produced in a medium that contained no carbohydrate and in which an acid reaction was not developed They stated that the amines can be thought of as buffers to reaction, and that their production from amino-acids is a protective mechanism which is resorted to when the accumulation of hydrogen ions within the organism's protoplasm threatens to destroy its life In addition, they showed that the production of histamine from histidine may be either appreciably slowed or stopped altogether by forcing *B. coli* to grow anaerobically ¹⁴ Weyl ¹⁵ showed that the putrefactive organisms, under conditions prevailing in the intestine, i. e., in the absence of oxygen, produce large quantities of phenols from tyrosine

It is reasonable to assume that, with the presence of amino-acids other than tyrosine, under the altered conditions mentioned, amines other than tyramine, notably histamine, may be produced in the intestine Histamine is antagonistic to tyramine in its action It produces intense stimulation of tone and rhythm of the smooth muscles, it lowers the blood pressure by dilating capillaries ¹⁶ and because of its power as a

11 Raper, H. S., and Speakman, H. B. *Biochem. J.* **20** 69 and 735, 1914

12 Folin and Denis. *J. Biol. Chem.* **22** 309, 1915

13 Hanke, M. T., and Koessler, K. K. *J. Biol. Chem.* **59** 858, 1924

14 Hanke and Koessler. *J. Biol. Chem.* **39** 581, 1919

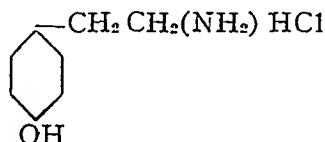
15 Weyl. *Ztschr. f. physiol. Chem.* **3** 312, 1879

16 Sollmann, T. *A Manual of Pharmacology*, Philadelphia, W. B. Saunders Company, 1927

stimulant to smooth muscles, it may, in considerable amounts, produce diarrhea and vomiting¹⁷ The production of histamine along with tyramine is important because of the antagonistic action between these two agents If it proceeds at a slow rate and in quantities sufficient for the effects of one to be neutralized by the effects of the other when both are absorbed, and if the rate of destruction is the same, then it may be assumed that few or no symptoms will result If, however, there should be some disparity between the production, absorption or destruction of either of these bases, then it is conceivable that the resulting symptoms would depend on which of the bases was present in excess

THE PHARMACOLOGIC ACTION OF TYRAMINE

Tyramine, as has been mentioned, is a base in which the action resembles that of epinephrine It is the hydrochloric acid salt of para-hydroxylphenylethylamine and is found in ergot Its structural formula resembles that of tyrosine and epinephrine quite closely



In action, according to Sollmann,¹⁶ it is not as powerful as epinephrine, but is more persistent It elevates the blood pressure, slowing the heart reflexly, and constricts the bronchioles It sometimes stimulates gastric secretion (in cats only) Hewlett¹⁸ reported that 20 mg injected in man produces a rise in the systolic blood pressure, the diastolic being only slightly elevated, if at all Subcutaneous injections in susceptible persons produce symptoms such as are found in exophthalmic goiter, namely tremor, palpitation and anxiety McCarrison⁴ concluded, as a result of experiments on the effects of ingestion of tyramine and histamine in pigeons and rats, that tyramine may possibly produce exophthalmos

How this powerful agent is detoxified is not altogether clear Hare¹⁹ expressed the belief that a definite enzymatic system is present in the liver for effecting rapid detoxication of excessive tyramine absorbed from the intestine by deamination and oxidation This seems to offer a fairly logical explanation of the fate of this substance

Tyramine, then, is a chemical agent that most probably plays an important part in the production of many of the symptoms in exophthalmic goiter The responsibility for practically all of the symptoms

17 Mellanby, quoted by Alvarez, W C *Physiol Rev* **4** 352, 1924

18 Hewlett, A W The Action of Tyramine, *Arch Int Med* **21** 411 (March) 1918

19 Hare, M L C *Biochem J* **22** 968, 1928

in this disease may be placed on tyramine, epinephrine and thyroxine, all derived from the amino-acid tyrosine in abnormal quantities by an irregular metabolism

SUMMARY

The hypothesis is advanced that exophthalmic goiter is primarily a disturbance resulting from a long-continued toxic process in the intestinal tract. This process not only damages the thyroid gland to the end that varying amounts of its functioning tissue are destroyed, but causes a faulty and irregular metabolism of the amino-acid tyrosine, so that an excess of thyroxine, epinephrine and tyramine is produced. These conclusions are reached in view of (1) the inadequacy of the thyrogenic theory of the disease, (2) the work of McCarrison on the effects of toxic material in the intestinal tract on the thyroid gland, (3) the close relationship between the chemical constitution of thyroxine, epinephrine and tyramine, (4) the common source of these three substances, viz, tyrosine, (5) the changes in the normal tyrosine-tyrosinase reaction and the decarboxylation process for conversion of tyrosine to phenols, with resulting overproduction of the base tyramine, and (6) the pharmacologic action of tyramine.

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THE ELIMINATION OF PHENOLSULPHONPHTHALEIN BY THE KIDNEY

THE INFLUENCE OF PATHOLOGIC CHANGES IN THE LIVER ~

J P HANNER, M D

AND

G H WHIPPLE, M D

ROCHESTER, N Y

Many years ago when Rowntree and Geraghty¹ were investigating the elimination of phenolsulphonphthalein in abnormal renal conditions, it was observed that certain cases of intoxication in pregnancy showed an unusually high degree of elimination. It was suspected that these obstetric cases were complicated by some abnormality of the liver, which interested Dr Whipple, who at that time was occupied with a study of experimental chloroform poisoning and hepatic injury².

Subsequently, on several occasions in experiments dealing with experimental chloroform poisoning in dogs, it was observed that the renal elimination of phthalein was unusual. This applied to both phenolsulphonphthalein (renal function) and phenoltetrachlorophthalein (hepatic function³). Preliminary experiments recently (1926) carried out in this laboratory by Dr D J Stephens and Dr F S Hassett, were in accord with those tabulated in this paper. During the following year (1927), Dr J M Scott and Dr D A Weir completed a few observations of similar nature.

As it was obvious that hepatic injury modified the elimination of phenolsulphonphthalein by the normal kidney, we decided to study carefully the mechanism of this unexpected reaction. From the standpoint of interpretation of the elimination of phthalein by the normal or abnormal kidney, it would seem that a complete understanding of this phenomenon would be of value to the clinician who must evaluate the figures for phthalein in terms of renal dysfunction.

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* From the Department of Pathology, the University of Rochester School of Medicine and Dentistry

1 Rowntree, L G, and Geraghty, J T. J Pharmacol & Exper Therap **1** 579, 1909

2 Whipple, G H, and Sperry, J A. Bull Johns Hopkins Hosp **20** 278, 1909

3 Whipple, G H, Peightal, T C, and Clark, A H. Bull Johns Hopkins Hosp **24** 343, 1913

It was first shown by Rowntree and Geraghty¹ that the liver was capable of excreting phenolsulphonphthalein. The dye appeared in the bile within an hour after the intravenous injection of 1 Gm of phenolsulphonphthalein. Since only the faintest traces of phthalein could be found in the stools of animals, they concluded that a portion excreted in the bile is reabsorbed by the intestines and excreted by the kidneys.

While attempting to discover the fate of phthalein injected into animals, Kendall⁴ found that when he mixed the dye with ground body tissue *in vitro*, after some hours it was partially reduced to a colorless substance. This occurred to the greatest extent when oxygen was eliminated from the mixture and when the liver, rather than the other organs, was used. He concluded that the liver is capable of destroying phthalein. Braasch and Kendall⁵ stated that phenolsulphonphthalein may be destroyed by mixing it with body tissues *in vitro* when oxygen is absent, but for this to occur in life, such a degree of anoxemia must be present that death is impending. They showed that alkalosis tended to increase the urinary output of phenolsulphonphthalein, whereas acidosis decreased it. Marshall and Vickers⁶ were able to recover 16 per cent of phenolsulphonphthalein from the liver of dogs killed fifteen minutes after 180 mg of the dye had been injected, thus showing a marked affinity of the liver for phthalein.

After observing marked variations in the urinary output of phenolsulphonphthalein in normal persons, Major⁷ investigated further the rôle of the liver in the destruction and retention of this dye. In rabbits he found a fairly uniform excretion, whether the phthalein was injected subcutaneously, intravenously or intrapleurally. However, when it was injected into the substance of the liver, a great reduction in the amount excreted in the urine occurred. When the dye was introduced into the portal vein, the amount eliminated in the urine was much less than when it was injected into the vena cava.

Moller and Lundsgaard⁸ expressed the belief that the liver plays a part in the elimination of phthalein. They recovered from 1 to 3 per cent of the dye from the duodenal contents of three normal persons and none from five persons with hepatic disease. They investigated the fate of the dye excreted by the liver, and found that when phthalein was given by stomach tube only from 1 to 8 per cent could be recovered.

4 Kendall, E. C. Phenolsulphonphthalein, *J. A. M. A.* **68** 343 (Feb. 3) 1917.

5 Braasch, W. F., and Kendall, E. C. *J. Urol.* **5** 127, 1921.

6 Marshall, E. K., Jr., and Vickers, J. L. *Bull. Johns Hopkins Hosp.* **34** 1, 1923.

7 Major, R. H. The Influence of the Liver on Phenolsulphonphthalein Excretion, *J. A. M. A.* **81** 1362 (Oct. 20) 1923.

8 Moller, E., and Lundsgaard, C. *Acta med. Scandinav.* **63** 277, 1926.

in the urine and, as a rule, only a trace in the stools. They also found that the contents of the stomach *in vitro* did not destroy phthalein, whereas the feces did. In a series of patients with hepatic disease, these investigators⁹ found that the elimination of phenolsulphonphthalein by the kidneys was prolonged and decreased. However, Chabanier and Gaume¹⁰ stated that these patients showed evidence of renal insufficiency as well as hepatic disease. This would perhaps explain why the excretion of phenolsulphonphthalein was decreased rather than increased as one would be led to expect.

In a series of cases of obstructive jaundice without complicating renal disease, Abrahamson¹¹ did not note either a decrease or an increase in the output of phenolsulphonphthalein.

Recently, while our experiments were in progress, those carried out by Bernheim¹² and Olivet and Prufer¹³ and summarized by Schlayer,¹⁴ in which the distribution of phthalein in the various tissues of the body was studied, came to our attention. They showed that thirty minutes after injection, the blood was practically free from phthalein, the dye was recovered subsequently in the various tissues of the body. Olivet and Prufer found that the tissues of the kidneys, liver and skin showed the most marked affinity for phthalein. Traces of dye were found elsewhere, except in the brain and spinal fluid. In a pregnant dog none was found in the placenta nor in the amniotic fluid. They expressed the belief that as phthalein is excreted, the tissues gradually give up their store, and eventually most of the dye is excreted, the chief routes being the urine and the bile. They suggested that perhaps small amounts may be excreted by the skin, but this was not investigated. Their work led them to believe that from 20 to 30 per cent of the dye is excreted by the liver, and that the greater part of this is reabsorbed from the intestines, although when the dye was given by stomach tube, they could recover only small amounts in the urine. In a case of cirrhosis, they recovered from the urine 80 per cent of the amount of dye injected after one hour, and found that none could be regained from the duodenal contents. Olivet¹⁵ recovered 90 per cent of the phthalein injected after two hours and 99 per cent after four hours from a dog in which the ductus choledochus had been tied for twenty-four hours. At autopsy, an extract of the

9 Møller, E., and Lundsgaard, C. *Acta med Scandinav* **63** 268, 1926.

10 Chabanier, H., and Gaume, P. *Bull Soc franç d'uro* **6** 69, 1927.

11 Abrahamson, H. A. Excretion of Phenolsulphonphthalein in Obstructive Jaundice, *Arch Int Med* **37** 291 (Feb.) 1926.

12 Bernheim, E. *Ztschr f klin Med* **104** 240, 1926.

13 Olivet, J., and Prufer, J. *Ztschr f klin Med* **108** 653, 1928.

14 Schlayer, Carl R. *Ztschr f Urol* **23** 621, 1929.

15 Olivet, J. *Ztschr f klin Med* **108** 665, 1928.

organs did not contain dye. They concluded that if the excretory and storing functions of the liver are blocked, the kidneys compensate and are able to excrete larger amounts of the dye. Tada¹⁶ pointed out that in the case of dyes excreted by both the kidneys and the liver, if one path of excretion is impaired, the other compensates and excretes more than its normal amount. This seems to be true for phenolsulphonphthalein when excretion by the liver is impaired.

METHODS

The general methods utilized were similar to those used by other investigators in this field. The solution of phthalein was made up as originally described by Rowntree and Geraghty so that 1 cc contained 6 mg of phenolsulphonphthalein. Only healthy, active, female dogs were used. In all instances the phthalein was injected into the jugular vein. Before each injection the bladder was emptied by catheter, and this urine was examined for albumin and microscopically for evidence of renal disease. Only dogs without evidence of renal disease were used. Unless otherwise noted, only 1 cc of phenolsulphonphthalein was injected. This was measured with a 1 cc pipet into a small dish. The pipet was then rinsed with physiologic solution of sodium chloride until no trace of the phthalein remained. The whole solution was then drawn up in a 10 cc syringe. After the injection of phenolsulphonphthalein, the dogs were given 500 cc of tap water by gavage in order to assure a fairly uniform and copious flow of urine. The urine was collected after one and two hours by means of a catheter, and the bladder was washed with 60 cc of warm tap water after each catheterization in order to obtain all traces of phenolsulphonphthalein in the bladder. As a rule, the urine was not collected later than two hours after the administration of dye, since after this time only small amounts are excreted, and because this is the time limit usually followed in clinical studies.

The collected urine was made alkaline with sodium hydroxide and diluted with distilled water to 1,000 cc after the first hour and to 500 cc after the second. This solution was then filtered and read in a Dubocq colorimeter against a standard containing 3 mg of phthalein per thousand cubic centimeters. The standard was freshly made twice a week. As a rule, no difficulty was experienced in matching the colors. When this happened, urine was added to the standard until a match could be obtained, the dilution being taken into account when the calculations were made.

In the dogs in which the common ducts were tied and the urine was highly colored with bile, we used the following method for precipitating the bile pigment. The urine was made alkaline by the addition of concentrated ammonia, and to each 50 cc of urine, 10 cc of a 10 per cent solution of calcium chloride was added. This was then centrifugated, and the clear supernatant fluid containing the phenolsulphonphthalein poured off. The precipitate was repeatedly washed with distilled water and centrifugated until the pink color could not be detected in the supernatant fluid. These washings were added to the original sample, diluted and compared in the usual way. As a rule, comparison with the standard was good. As a control, when phenolsulphonphthalein was added to varying amounts of urine and bile and treated as has been described we found that from 85 to 100 per cent of the dye could be recovered. The error increased with the amounts of urine and bile added.

The same procedure was followed in the case of bile containing phenolsulphonphthalein. Each 10 cc of bile was diluted to 50 cc with distilled water, and made alkaline with concentrated ammonia. To this we added 10 cc of the solution of calcium chloride. This was centrifugated, washed and diluted as described for the urine. Here, however, the matches in color were not quite as good. In control experiments in which from 10 to 30 cc of bile was added to 3 mg of phenolsulphonphthalein, we found that we were able to recover from 85 to 95 per cent of the dye by this method.

To produce chloroform poisoning, the dogs were starved for from twenty-four to sixty-four hours. A light surgical anesthesia was produced for from sixty to ninety minutes with chloroform. Following this, they did not receive food for twenty-four hours. An indication of the degree of hepatic damage was obtained by the determination of fibrin in some instances and by the icterus index in others.

The production of satisfactory damage to the liver by the administration of phosphorus was found to be difficult, because of the variations occurring in the reactions of the dogs to the solution used. The results of these experiments are inconclusive though in several instances suggestive. Stick phosphorus was dissolved in olive oil, 1 cc 10 mg. This was injected subcutaneously or intramuscularly.

EXPERIMENTAL OBSERVATIONS

We shall cite only a few experiments which illustrate characteristic reactions to chloroform poisoning. We have on record a large number of similar experiments, and believe that the reactions tabulated here adequately show the character of the reaction and are fair examples of a considerable series.

As one might expect, the higher figures were observed in the more severe cases of hepatic injury due to chloroform and they persisted longer than in the cases of mild poisoning.

Table 1 shows the usual reaction to chloroform poisoning with a rise of from 10 to 15 points in the figures for the elimination of phthalein in the urine. The figures for fibrin prove beyond a doubt¹⁷ that a fairly severe hepatic injury was produced by sixty minutes of chloroform anesthesia. It is well known¹⁷ that within a few days the liver promptly repairs this type of injury, and that the blood fibrin then returns to normal. There is always a rise in the icterus index (table 2). In this experiment (table 1), the high values for the elimination of phthalein lasted four days and then fell toward normal.

As a control for the experiments on hepatic injury due to chloroform poisoning, we recorded the negative reaction to long periods of ether anesthesia preceded by fasting.

On the four days following the second experiment with chloroform anesthesia on the same dog (table 1), there were identical reactions and high figures for the elimination of phthalein. In spite of a longer fast and a somewhat longer duration of the anesthesia, the injury

17 Foster, D. P., and Whipple, G. H. *Am J Physiol* 58:407, 1922.

TABLE 1—*Severe Hepatic Injury and the Elimination of Phthalein in the Urine of Dog 29-32, Weight, 18.5 Kg*

Date	Output of Phenolsulphophthalein, per Cent			Output of Urine, Cc			Fibrin Mg per 100 Cc
	First Hour	Second Hour	Total 2 Hours	First Hour	Second Hour	Total 2 Hours	
11/19	75	9	84	35	124	159	
11/22	66	11	77	20	30	50	
11/23	65	7	72	30	51	81	264
11/25	Chloroform anesthesia, 60 minutes, fasting, 24 hours						
11/26	84	11	95	30	121	151	221
11/27	82	11	93	57	170	227	76
11/29	86	10	96	150	200	350	125
11/30	80	6	86	38	105	143	202
12/ 2	69	11	80	95	160	255	
12/ 3	71	10	81	95	233	328	
12/ 7	69	8	77	95	205	300	
12/17	64	16	80	10	25	35	
12/20	Ether anesthesia, 60 minutes, fasting, 24 hours						
12/22	72	8	80	60	300	360	
12/31	64	10	74	15	140	155	
1/ 1	66	10	76	30	140	170	
1/ 6	Ether anesthesia, 60 minutes, fasting, 64 hours						
1/ 7	69	13	82	15	185	335	
1/ 9	69	11	80	28	175	203	
1/11	72	7	79	45	250	295	
1/13	65	11	76	30	200	230	
1/14	66	14	80	65	235	300	
1/15	Chloroform anesthesia, 75 minutes, fasting, 51 hours						
1/16	78	15	93	85	63	148	
1/17	79	9	88	50	43	93	127
1/18	80	7	87	150	228	278	160
1/19	85	10	95	95	200	295	
1/21	77	3	80	105	139	244	
1/23	64	10	74	15	50	65	

TABLE 2—*Hepatic Injury and the Elimination of Phthalein in the Urine*

Date	Output of Phenolsulphophthalein, per Cent			Output of Urine, Cc			Icterus Index
	First Hour	Second Hour	Total 2 Hours	First Hour	Second Hour	Total 2 Hours	
Dog 29-32, weight 18.5 Kg							
10/17	72	3	75	90	200	290	
10/22	69	9	78	30	130	160	
10/23	64	8	72	70	180	250	
10/24	56	17	73	25	90	115	
10/25	Chloroform anesthesia, 60 minutes, fasting, 25 hours						
10/26	63	11	74	20	15	35	
10/28	88	11	99	90	150	240	
10/29	78	19	97	130	100	230	
10/30	88	11	99	60	30	90	
10/31	89	10	99	65	50	115	
11/ 6	69	9	78	20	50	70	
11/ 8	70	10	80	60	135	195	
11/ 9	71	15	86	15	39	54	
11/11	75	10	85	29	91	120	
11/16	57	14	71				
Dog 29-322, weight 17 Kg							
7/ 2	67	10	77	50	100	150	
7/ 3	63	10	73	69	160	229	
7/12	69	9	78	148	270	418	
7/14	61	11	72	30	250	280	3
7/14	Chloroform anesthesia, 75 minutes, fasting, 51 hours						
7/15	77	11	88	160	320	480	
7/16	72	19	91	105	290	395	20
7/17	78	11	89	140	140	280	
7/19	62	16	78	150	160	310	8
7/21	66	12	78	85	250	335	3
7/22	63	11	74	95	210	305	

to the liver, as indicated by the values for fibrin which were depressed, was probably not as great as in the first experiment on this dog in which the values for fibrin were very low (table 1) This statement is based on wide experience with necrosis (due to chloroform) and repair of the liver under various controlled conditions¹⁸

Table 2 shows two more typical experiments with chloroform anesthesia, injury to the liver and an increased elimination of phthalein in the urine The figures for the elimination of phthalein are higher for dog 29-32 than for dog 29-322, which would indicate a somewhat higher grade of hepatic injury, but we have no figures for the fibrin to prove it Dog 29-32 was sick for two days during which traces of bile showed in the urine, but she recovered promptly Dog 29-322 was not clinically ill at any time As a general rule, younger dogs are more susceptible to chloroform poisoning than older animals, and

TABLE 3—*Mild Hepatic Injury and the Elimination of Phthalein in the Urine of Dog 29-227, Weight, 16 Kg*

Date	Output of Phenolsulphophthalein, per Cent			Output of Urine, Cc			Fibrin Mg per 100 Cc
	First Hour	Second Hour	Total 2 Hours	First Hour	Second Hour	Total 2 Hours	
1/11	60	9	69	55	210	265	298
1/14	64	8	72	95	278	373	294
1/16	55	9	64	20	160	180	
1/17	63	10	73	78	235	313	
1/17	Chloroform anesthesia 75 minutes, fasting, 51 hours						
1/18	69	10	79	90	208	298	346
1/19	90	9	89	120	190	310	
1/21	78	10	88	50	195	245	
1/23	65	6	71	3	58	61	
1/28	55	16	71	60	309	369	
2/ 7	66	13	79	58	258	316	
2/ 9	67	10	77	60	220	280	

a longer period of fasting usually renders a dog more susceptible, but there are individual differences which at present we cannot explain The icterus index in the second experiment (table 2) showed a rise that is invariably present in cases of hepatic necrosis of moderate or slight grade In this dog the elevated elimination of phthalein lasted only three days

Table 3 shows a mild case of hepatic injury due to chloroform, as indicated by the rise in the figures for fibrin This dog (29-227) took the chloroform anesthesia poorly and was given less chloroform than usual, which may explain the slight hepatic injury associated with seventy-five minutes' anesthesia We have repeatedly observed that slight hepatic necrosis, like necrosis of tissue elsewhere (sterile abscess), will cause a rise in the blood fibrin, whereas moderate or severe hepatic

18 Davis, N C Liver Regeneration Following Chloroform Injury as Influenced by Various Diets, Arch Int Med 23 711 (June) 1919

necrosis caused by chloroform will cause a moderate or notable decrease in blood fibrin, due in part to hepatic dysfunction and insufficiency. The rise in the elimination of phthalein was only moderate and definitely less than the figures recorded in tables 1 and 2. None of these dogs showed an albuminuria before or after the chloroform anesthesia.

In this group of experiments urea clearance tests were performed, but owing to inexperience with the methods, we have not included them in this report. In general, however, our results suggested an increased clearance after the administration of chloroform. As a rule, the blood urea showed a drop. As far as we know, there is no report in the literature on the variations from normal of the urea clearance test in cases of hepatic damage with normal kidneys. We hope to give this subject further study.

In order to bring additional evidence that the liver in dogs is impaired in its ability to excrete phthalein after chloroform anesthesia, a different type of experiment was performed.

The normal level of the output of phthalein was determined. The dog was then starved and given chloroform in the usual manner. The excretion of phthalein in the urine was determined twelve and thirty-six hours after the administration of chloroform, and was found to be increased during the two hour period from the normal of from 70 to 75 per cent to 88 per cent, as in similar experiments already tabulated. Forty-eight hours following the chloroform anesthesia, the dog was given a general ether anesthesia, a cannula was inserted into the common duct, and the bile and urine were collected over a two hour period following the injection of 60 mg of phthalein. The flow of bile was greatly decreased, only 2 cc being collected, and no trace of phthalein could be demonstrated in it. The kidneys excreted 40 cc of urine, which contained 25 per cent of the dye. The dog was killed under ether anesthesia. At autopsy, the liver showed typical marked central necrosis, but the other organs were normal. An alcoholic extract of macerated liver gave no trace of the phthalein, whereas an extract of the kidneys contained large quantities of it. In similar experiments, only without a preceding chloroform anesthesia, dogs under ether anesthesia showed a flow of bile containing from 9 to 10 per cent of the phenolsulphon-phthalein originally injected.

Phosphorus poisoning causes a characteristic hepatic injury, but the experiments are difficult to control with the accuracy possible in experiments on chloroform poisoning. The usual difficulties were encountered in this type of experiment, and we record no experiment in detail as the change in the elimination of phthalein was much less marked. In several dogs with moderate phosphorus poisoning, the elimination of phthalein rose somewhat above control levels, but not to the same extent noted in hepatic injury due to chloroform.

The Elimination of Phthalein in the Bile of Normal Dogs Under Ether Anesthesia—Obviously dogs under ether anesthesia are not strictly normal, nor are dogs with biliary fistulas of many weeks' dura-

tion, yet from experiments on both types evidence as to how much phenolsulphonphthalein is eliminated by the liver may be gained. The following two experiments give evidence that the normal dog under ether anesthesia will eliminate 10 per cent or more of the injected phthalein through the bile during a period of two hours.

EXPERIMENT A (dog 29-4) —At 10 25 a m, 150 cc of bile was given by stomach tube to increase the flow of bile. At 11 25 a m, the administration of ether was begun. A cannula was inserted in the common bile duct and in the urinary bladder. At 12 38 p m, 60 mg of phenolsulphonphthalein was injected into the jugular vein, followed by 300 cc of physiologic solution of sodium chloride injected slowly. At 12 45 p m the phthalein made its first appearance in the bile, and at 12 48 p m, its first appearance in the urine. At 2 38 p m, the dog was killed under ether anesthesia.

Examination of 30 cc of urine two hours after the injection of phenolsulphonphthalein showed 74 per cent of the dye. Five cubic centimeters of bile from the cannula returned 4 per cent of phenolsulphonphthalein, while 15 cc of bile from

TABLE 4—*Biliary Fistula and the Elimination of Phthalein*

Phenolsulphonphthalein								
Dog *	Date	Injected Intraven- ously, Mg	Output, per Cent			Flow of Urine, Cc		Biliary Flow, Cc in 6 Hours
			Urine 2 Hours	Urine 6 Hours	Bile 6 Hours	2 Hours	6 Hours	
29-8	6/12	60	95	99	Trace	245	645	18
	6/13	60	88	93	Trace	550	970	11
	6/14	60	83	89	Trace	140	235	27
29 169	6/12	60	80	84	7	285	435	14
	6/13	60	82	85	9	302	418	15
	6/14	60	83	86	7	250	415	33

* An operation for biliary fistula was performed on dog 29-8 on February 20 and on dog 29-169 on February 25.

the gallbladder returned 6 per cent. The total recovery of phenolsulphonphthalein was 84 per cent of the amount originally injected into the dog.

EXPERIMENT B (dog 29-244) —At 1 30 p m, 150 cc of bile was given by stomach tube to dog 29-244, which weighed 5 Kg. At 2 p m, anesthesia was begun by the injection of iso-amyl-ethyl barbituric acid, intraperitoneally, supplemented with ether. Cannulas were inserted into the common duct and the urinary bladder, and the cystic duct was ligated. At 2 50 p m, 60 mg of phenolsulphonphthalein was injected intravenously. At 2 58 p m, it made its first appearance in the bile, and at 3 p m, its first appearance in the urine, there was, however, a lack of diuresis. At 4 50 p m, the dog was killed under ether anesthesia.

Two hours after the injection of phenolsulphonphthalein had been made in the total collection of 50 cc of urine there was 67 per cent of phthalein. In the total collection of 8 cc of bile there was 9 per cent of the dye. The bile of the gallbladder did not show phthalein. There was, therefore, a total recovery of 76 per cent of the phenolsulphonphthalein injected.

At autopsy, the tissue of the liver and the kidney of both dogs was found to be normal in gross and in histologic sections.

To supplement the short experiments on the elimination of phenolsulphonphthalein in the bile during ether anesthesia, we utilized dogs

with closed sterile biliary fistulas. These dogs were operated on by Dr H P Smith according to a technic described elsewhere¹⁹. Table 4 shows that biliary fistulas may vary widely in their capacity to eliminate phenolsulphonphthalein in the bile. It is known that these fistulas may lose their capacity to eliminate dyes. Both these dogs had been under observation with a daily collection of bile for about four months. In some instances the presence of infection in the biliary passages may be partly responsible for the difference. Whatever the cause, from the biliary fistula of one dog there was but a trace of phthalein in the bile and a distinctly high output in the urine. In the biliary fistula of

TABLE 5—*Obstruction of the Bile Duct and the Elimination of Phthalein in the Urine*

Date	Output of Phenolsulphophthalein, per Cent			Output of Urine, Cc			Icterus Index
	First Hour	Second Hour	Total 2 Hours	First Hour	Second Hour	Total 2 Hours	
Dog 29-227, weight 16 Kg							
5/19	66	8	74	60	250	316	
5/21	61	11	72	60	285	340	
5/23	62	9	71	105	205	310	4
5/24	Common duct ligated						
5/26	80	5	85	18	165	183	24
5/28	74	12	86	38	360	434	70
5/30	78	10	88	87	420	507	70
6/ 2	71	13	84	93	214	307	70
6/ 4	74	10	84	57	170	227	
6/ 9	81	12	93	33	124	157	
6/10	67	17	84	65	198	263	
6/16			91			250	
Dog 29-307, weight 13 Kg							
7/15	66	7	73	190	70	260	
7/17	67	9	76	130	255	385	
7/18	66	10	76	90	225	315	4
7/19	Common duct ligated						
7/21	67	11	78	109	46	155	8
7/22	76	11	87	133	52	185	20
7/24	57	33	90	70	79	149	40
7/26	72	13	85	132	130	262	40
7/29	81	12	93	190	85	275	45
8/ 1	74	9	83	200	70	270	70
8/ 5	71	12	83	85	140	225	70

dog 29-169 (table 4), the output of phthalein was between 7 and 9 per cent in the bile and between 80 and 83 per cent in the urine. On June 14, both dogs were given bile by mouth, with a moderate chologogue effect which did not modify the elimination of phthalein in the biliary fistula.

Obstruction of the Bile Duct—Dogs with obstructed common ducts show a definite rise in the elimination of phthalein by way of the kidneys (table 5). These figures are not quite as high as they are in dogs with marked hepatic injury due to chloroform, and to explain

¹⁹ Smith, H P, Groth, A H, and Whipple, G H. J Biol Chem **80** 659, 1928.

the difference two factors are suggested 1 In heavily pigmented urine, the phthalein is more difficult to read, and the method of separation of the bile pigments carries down a little phthalein 2 Even in an obstructed common duct some phthalein is taken into the epithelium of the liver and the bile canaliculi

We noted the expected rise in the icterus index After completion of these observations the dogs were killed with ether Autopsy showed the usual picture associated with continued biliary obstruction The common bile ducts were completely occluded by the ligatures Except for bile stains, the kidneys and viscera were normal

Of similar nature is an experiment on a dog with an Eck fistula in which a closed sterile biliary fistula had been produced by Dr H P Smith in connection with other experimental work After a time, biliary obstruction developed in this dog (table 6), due to blocking of

TABLE 6—*Eck Fistula with Partial Obstruction of the Bile Duct and the Elimination of Phthalein in Dog 29-14, Weight, 13 ± Kg*

Date	Output of Phenolsulphonphthalein, per Cent			Output of Urine, Cc		
	First Hour	Second Hour	Total 2 Hours	First Hour	Second Hour	Total 2 Hours
2/11	91	5	96	70	86	156
3/ 3	87	4	91	80	75	155
3/ 4	67	15	82	90	240	330
3/ 5	77	6	83	85	100	185
3/ 6	Ether anesthesia 120 minutes					
3/24	90	7	97	55	215	270
4/ 4	80	5	85	165	240	405
4/ 8	84	3	87	160	115	275
4/29	78	6	84	100	131	281

the flow of bile in the tube of the fistula The dog remained in good health and eventually a partial drainage of bile was established into the duodenum Preoperative, control tests made with phthalein were not available

In this dog the elimination of phthalein by the way of the kidney was high (table 6), and held about the same level as that noted in the dogs with obstructed common bile ducts This was to be expected in spite of a slight drainage of bile during the last part of the experiment A liver with an Eck fistula is known to be subnormal functionally, and there is less elimination through the liver on this account On March 6, during the period of ether anesthesia (table 6), the bile ducts were explored The dog died on March 30 Autopsy showed the atrophied liver usually seen in the case of an Eck fistula, with a little fatty change The kidneys were normal

The Effect of Cholagogue and the Oral Administration of Phenolsulphonphthalein—We suspected that an active cholagogue effect

might sweep more phenolsulphonphthalein into the bile than was usual and therefore decrease the urinary output. We have already noted (table 4) that in dogs with biliary fistulas, whether a cholagogue is used or not, there is no difference in the elimination of phthalein in the bile. In normal dogs carefully standardized for the elimination of phthalein by way of the kidney, we have repeatedly tested the influence of large doses of bile given by mouth. Whether or not there may be a slight increase in the output of phthalein in the bile under these conditions, there is a uniformly normal urinary output of phthalein. These dogs were given 150 cc of bile by stomach tube one hour before the phthalein was given intravenously. The phthalein eliminated in the urine was always within control limits.

The gastro-intestinal tract absorbs a limited amount of phenolsulphonphthalein given by mouth. In a series of dogs in which 30 mg of phenolsulphonphthalein was given by stomach tube, only from 3 to 5 per cent appeared in the urine and only traces in the feces. Obviously, intestinal absorption plays no rôle in any of the reactions that we have studied. In a normal dog, granting 20 per cent elimination of phthalein by way of the bile, we could expect only 5 per cent of this amount to be absorbed. This amount of phenolsulphonphthalein is within the limits of error of any method of analysis.

COMMENT

It is obvious that the liver of the normal dog excretes from about 10 to 15 per cent of the usual dose of phenolsulphonphthalein, and when this route of escape is blocked, the surplus appears in the urine, giving figures proportionately greater, as recorded in the various tables cited. Phthalein which escapes into the gastro-intestinal tract is absorbed only to a limited degree—not in excess of 5 per cent of the amount secreted into the duodenum, so that reabsorption from the bile can be dismissed as a factor of no importance.

Clinically, this reaction may have some significance, as an unusually high elimination of phthalein in the urine would suggest an abnormality in the liver. When abnormalities are present in both the liver and the kidney of a patient, careful study might solve the puzzle, but judgment would indeed be difficult. However, if the clinician understood these possibilities, he would not be led astray by an unusual elimination of phthalein in the urine.

SUMMARY

From our experiments it is clear that in dogs with necrosis of the liver due to chloroform poisoning there is a distinct rise in the elimination of phenolsulphonphthalein by the normal kidney. A rise

in the elimination of phthalein from a control level of from 75 to 78 per cent, to from 90 to 97 per cent may be noted. With repair of the hepatic injury, the elimination of phthalein returns to normal. Phosphorus poisoning gives a similar but less striking reaction.

With experimental biliary obstruction in the dog, the same general reaction is noted, with a definite increase in the elimination of phenolsulphonphthalein by the normal kidney.

After hepatic injury due to chloroform, the dog's liver does not remove phenolsulphonphthalein from the blood stream and does not excrete it in the bile, whereas in a normal dog, the liver removes much phthalein from the blood, and about 10 per cent of the injected phthalein may be recovered from the bile within two hours.

A chronic biliary fistula and an Eck fistula may permit a smaller excretion of phenolsulphonphthalein in the bile and a corresponding rise in the elimination of phthalein in the urine.

There is no evidence that cholagogue, whether in the normal dog or in one with a biliary fistula, increases the elimination of phthalein by way of the bile, and consequently the urinary excretion of phthalein is unchanged.

Phenolsulphonphthalein given by mouth is absorbed and reappears in the urine only in quantities equal to from 3 to 5 per cent of the phthalein administered. Reabsorption, therefore, is a negligible factor when applied to the phenolsulphonphthalein eliminated through the bile into the duodenum.

From these experiments and the observations of other workers, it may be concluded that the elimination of phthalein by the liver and kidney under these conditions is identical in the dog and man.

Clinically, an unusually high renal elimination of phenolsulphonphthalein should suggest pathologic changes in the liver. Combined renal and hepatic disease calls for cautious analysis of the renal elimination of phenolsulphonphthalein.

TUMORS OF THE SUPRARENAL GLAND WITH SPECIAL REFERENCE TO CARCINOMA OF THE CORTEX

REPORT OF A CASE

JACOB MEYER, M D
AND
GERALD FRUMESS, M D
CHICAGO

Four syndromes are recognized as associated with changes in the suprarenal gland. The first, Addison's disease, is due to hypofunction of the suprarenal cortex as a result of disease, usually tuberculosis. This condition is a well recognized entity and need not be discussed here. The second picture is that seen as a result of tumor of the suprarenal medulla, its characteristic features result from metastatic phenomena, as described by Hutchison and Pepper. These will be discussed more fully in the section of this paper on pathology. The third is the recently described picture of cytotoxic degeneration of the suprarenal cortex, and may be found described in recent periodicals. The fourth syndrome is that described by Gallais¹ as "le syndrome génito-surrénal," and is seen in tumors of the suprarenal cortex with neoplastic tendencies.

To acquaint the physician better with this syndrome we shall report a case and emphasize the characteristic symptoms and signs of the picture. The desirability of early recognition of the tumor is obvious, especially in the light of recent reports on the surgical removal of tumors of the suprarenal capsule, with complete recovery.

REPORT OF A CASE

History—M. R., a white girl, aged 13, entered the service of Dr. A. Strauss complaining of pain in the chest and the abdomen, dermatitis, indigestion and epileptiform attacks.

She had felt well until eight weeks before, when she was seized with a severely sharp pain in the lower right side of the chest. A few minutes later she complained of pain in the abdomen, which was not a radiation from the pain in the chest. No nausea or vomiting occurred. Constipation had continued to the time of admission. The abdominal pain had recurred two or three times daily after the ingestion of any food.

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* From the Medical Service and Stomach Study Group, Michael Reese Hospital.

1 Gallais, Alfred. Le syndrome génito-surrénal, étude anatomo-clinique, These, Paris, 1912, no 225.

The dermatitis was of about five months' duration. It was an acneform rash, covering the face and trunk and not affecting the extremities.

Menstruation, which had started when the patient was 12½ years of age, was of the regular twenty-eight day type, each period lasting between three and four days. The menses had ceased three months before admission. Other facts in the history were irrelevant.

Physical Examination—The patient was extremely well developed and well nourished and did not seem to be acutely ill. Although only 13 years of age, she had the appearance of a person of 19 or 20.

A papular and pustular lesion was present on the face, the neck and the anterior portion of the chest and extended over the entire back to the buttocks. There were many comedones on the face, and moderate dermatographia. The facies was negroid, which was accentuated by hirsuties.

The breasts were slightly developed. The genitalia showed an abnormal growth of pubic hair, with a distinct tendency to masculine distribution.

The left border of the heart was 11 cm. to the left of the midsternal line in the fourth interspace, and 3 cm. to the right. The heart was probably displaced upward by a combination of enlarged liver and distended abdomen, rather than being itself enlarged. The tones were regular and of good intensity. There was a soft systolic blowing murmur at the base of the left lung. The blood pressure was 158 systolic and 85 diastolic.

The abdomen was full and somewhat distended. There was no fluid or rigidity.

The upper border of the liver reached the fourth rib, while the lower border was at the level of the umbilicus, the edge was felt to the left as far as the left nipple line. The edge and surface were irregular, there were several palpable nodules, and the consistency was increased.

The spleen was not palpable, and the kidneys were not felt.

The Wassermann and Kahn reactions were negative, the blood count showed leukocytosis, with an increase in polymorphonuclears. Chemical examination of the blood showed that it was normal, and the icteric index and van den Bergh reactions were negative. On two occasions the urine showed albumin and a few pus cells. A complete series of roentgenograms of the gastro-intestinal tract failed to disclose a pathologic process. A roentgenogram showed the right kidney to be somewhat enlarged, but with a smooth outline.

Course—During the patient's stay in the hospital, the liver seemed to be enlarging downward, particularly to the left. It was questionable whether or not the spleen was palpable. The right lobe of the liver seemed to be irregular, and had a stratified, steplike anterior surface.

A blood smear disclosed about 5 per cent immature leukocytes, most of them myelocytes.

Epigastric fulness and pain seemed to become more severe from day to day, but there was no qualitative distress from food. The patient was given hourly feedings of milk and cream, with additional small feedings of a soft diet, three times a day. She refused food so persistently that a duodenal tube was introduced for feeding.

About the eighth day after admission, the patient began to look more acutely ill. At 4 p. m. her temperature rose above normal for the first time, reaching 100 F., and her pulse rate was 116.

Little progress was made in the formation of a diagnosis. The icteric index and van den Bergh reaction practically ruled out hypertrophic biliary cirrhosis. The negative Wassermann reaction spoke against syphilitic cirrhosis or hepatitis.

The possibility of a myelogenous leukemia was considered in view of the finding of immature leukocytes, however, either a derangement in the physiology of the liver or leukocytosis might explain the presence of an occasional myelocyte. A vascular accident in a congenitally malformed liver might constitute the underlying pathology of the case. Cystic adenoma of the liver was also considered as a possibility. A possible endocrine disturbance was considered to explain the patient's overgrowth and the masculine distribution of hair.

One week after admission, signs and symptoms of intra-abdominal hemorrhage developed, and death occurred seven hours later.

Postmortem Examination—Autopsy was performed by Dr. Otto Saphir. The head was covered with a good growth of coarse, kinky, black hair. There was a marked growth of pubic hair. The skin was sallow. There were many discrete



Fig 1—Tumor of the suprarenal gland

small pustules on the forehead, chin and chest. The breasts were small, but the nipples and areolae were well developed. The abdomen was somewhat distended. The body from the pelvis down had the development of a 20 year old woman. The vulva was edematous and there was a slight degree of edema of the lower extremities.

The pleural and pericardial cavities did not contain excessive amounts of fluid or adhesions. The peritoneal cavity was filled with about 1,500 cc of bloody fluid. The liver extended to the level of the umbilicus. A large, spherical mass having a diameter of about 17 cm. was palpable in the region of the left kidney.

The heart was about normal in size. There were slight hypertrophy and dilatation of the left ventricle. The auricles, the right ventricle and the valvular apparatus appeared normal. Changes were not noted in the aorta.

The lungs were nearly normal in size, soft and air containing. On the visceral pleurae a few firm, raised, grayish nodules, having an average diameter of 2 mm., were found, which, on section, presented gray, granular surfaces.

Sections of the lungs were deep pink. There were a few areas that were slightly raised and that presented a grayish granular appearance. The larynx and trachea were normal.

The liver was markedly enlarged and weighed about 3 Kg. There was a tear at the inferior border of the left lobe, about 3 cm. in length. Many irregularly circular, firm, raised, pinkish-gray areas were seen beneath the capsule on all the surfaces of the liver. The tissue between these nodules was bluish red in areas and yellowish brown in other portions. On section, numerous raised, firm, yellowish-gray, granular masses were seen throughout. They varied in size from 1 to about 3 cm. The intervening tissue was yellowish brown. In some areas the central zones appeared as grayish-red dots, many of which were fused by confluence to form a prominent bluish-red network.

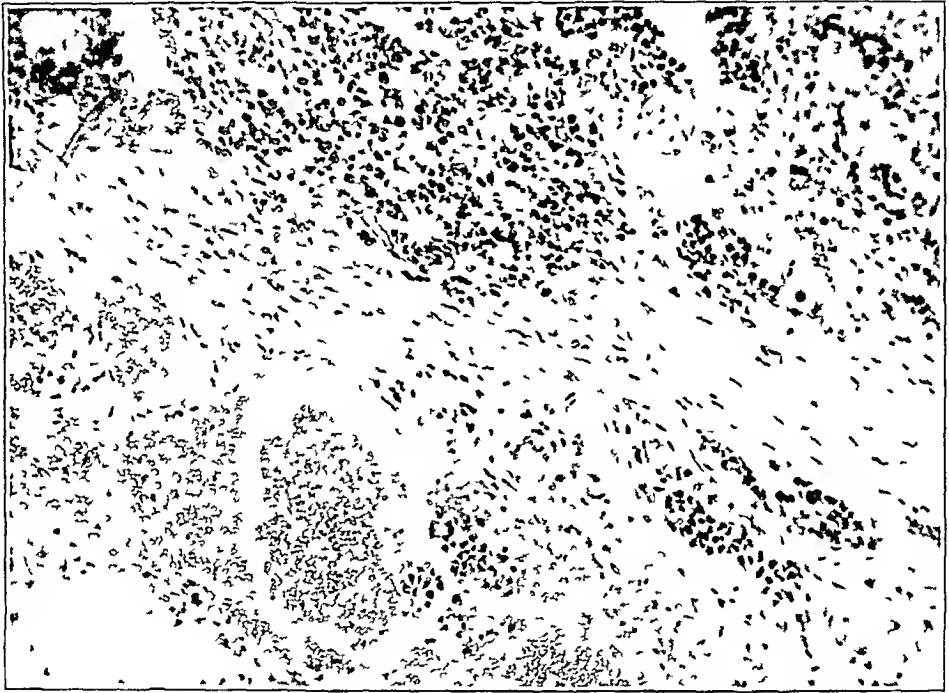


Fig 2—Histologic section of the tumor showing cells and areas of necrosis and degeneration

The spleen was normal in size. The capsule was smooth and bluish gray, and on section the cut surface was dark red, and numerous malpighian corpuscles could be seen.

The site of the left kidney was completely replaced by a tumor mass measuring 17 by 13 by 7 cm. This mass was covered by a thin fibrous capsule, which when separated disclosed the left kidney lying in a medial and posterior position. The left kidney was somewhat smaller than normal and was apparently compressed lateromedially. The capsule of the kidney was not involved by the tumor. It stripped with ease, revealing the surfaces of the kidney to be smooth and pale brown. The stellate veins were hyperemic. On section, the architecture of the cortex and the medulla was distinct. The pyramids were somewhat hyperemic. The right kidney appeared normal. The renal pelves, ureters and urinary bladder did not show gross changes.

The tumor was fairly soft and had a lobulated appearance. On section, broad bands of connective tissue were seen which divided the tumor into several large lobes. In areas this connective tissue appeared to be hyalinized, and in other portions, hemorrhagically discolored. The tumor tissue was yellowish gray, soft and very friable. It had a granular architecture. In portions the tumor tissue was compact and firm, while in other portions it was mushy.

The right suprarenal gland appeared normal.

The lymph nodes throughout the peritoneal cavity and those attached to the pericardial sac showed marked enlargement. About the hilus of the liver and attached to the serosa of the neck of the gallbladder were several lymph nodes. The nodes had an average diameter of about 1 cm. Most of them were soft and, on section, presented yellowish-gray, granular, cut surfaces.

The thyroid gland did not show gross pathologic changes.

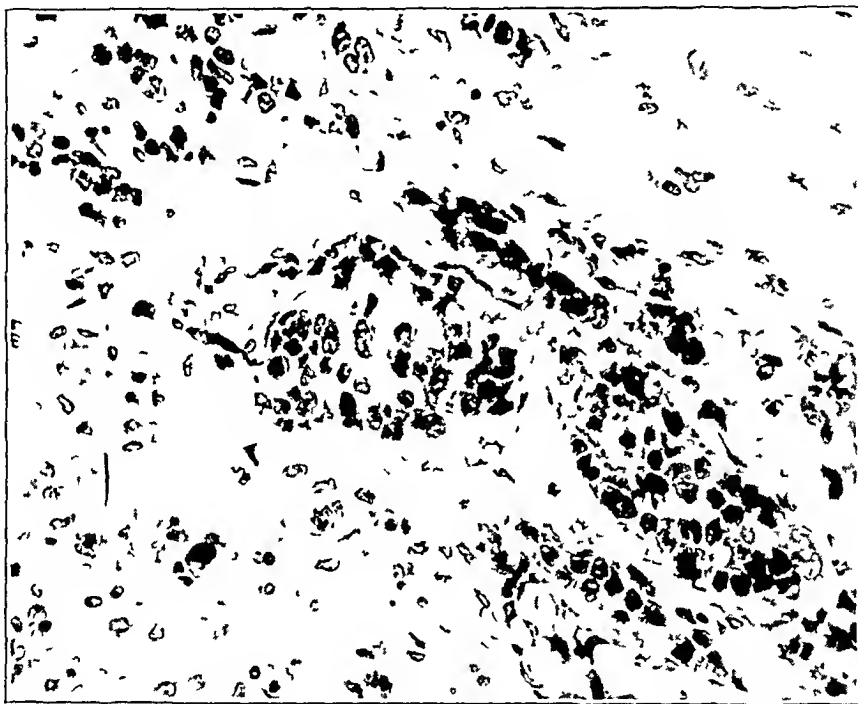


Fig 3—Microscopic section of the tumor showing carcinoma cells and areas of necrosis and degeneration

The uterus appeared to be maturely developed and nulliparous. The tubes and ovaries were normal.

The anatomic diagnosis was primary carcinoma of the left suprarenal gland with metastases to the pleurae, the liver and the peritoneal and mediastinal nodes, hemoperitoneum, slight hypertrophy and dilatation of the left ventricle, chronic passive hyperemia of the liver, lungs, kidneys and intestines, fat infiltration of the liver, precocious development, early bronchopneumonia, and virilism.

Microscopic examination was made by Dr Otto Saphir. Sections of the left suprarenal gland showed a marked new formation of cells in some of the fields. Most of these were apparently epithelial. They were very large and showed granular cytoplasm. Many cells were hexagonal, while others appeared more square. Some of the cells resembled those of the zona fasciculata. In general, the cells varied in size, form and staining quality. The nuclei stained a deep blue, and

most of them were vesicular and eccentrically situated. Many mitotic figures were found invading the tissue. Other areas showed an abundant amount of necrosis and hemorrhage, with only remnants of cells. Other fields showed cells invading the walls of veins, while in others the veins were filled with tumor cells. The sections showed little stroma between the tumor cells.

Microscopic examination of the lungs showed a few more or less circumscribed areas with an invasion of tumor cells similar to those in the left suprarenal gland. Some of these vessels in the section were filled with tumor cells.

Sections of the heart showed the muscle fibers to be somewhat larger than normal. A few fields showed an extension of the epicardial fat tissue into the myocardium.

Sections of the liver showed large nodules that were made up entirely of tumor cells. The necrosis here was slight, and therefore the shape of the tumor cells could be studied to great advantage. The surrounding liver tissue was markedly compressed.

Sections of the right suprarenal gland showed a large cortical adenoma. Pathologic changes were not noticeable. A section of the hypophysis did not show histologic changes.



Fig 4—Metastasis to the liver

SYMPTOMS

Though individual cases present marked variability in the character and intensity of the symptoms which they present, the picture of suprarenal cortical tumor is always so characteristic that the only excuse for failure to make an early diagnosis is lack of familiarity with the syndrome which Gallais has appropriately named "le syndrome g nito-surr nal."

The symptoms vary, first, depending on the age at which the tumor develops. Gallais, for instance, described four forms: (1) congenital, (2) early acquired, (3) menstrual and (4) obstetric. Apert² described

² Apert, E. Dystrophies en relation avec des l sions de capsules surrenales, hirsutisme et prog nia, Bull. Soc. de p diat. de Paris **12** 501, 1901, Sur l'hirsutisme, Bull. et mem. Soc. m d. d'h p. de Paris **49** 131, 1925.

five forms Hoskins³ simplified the classification somewhat, and described three forms (1) hypertrophy of the suprarenal cortex during fetal life, producing pseudohermaphroditism (illustrative of this form is a case reported by Quinby,⁴ in which he described a girl who was raised as a boy because of the masculine status and genitalia), (2) hypertrophy during early postnatal life, resulting in the production of pubertas praecox, and (3) hypertrophy after puberty, producing virilism or hirsutism.

Whereas other glandular dysfunctions, particularly those resulting from tumor of the pineal gland and alterations of the sexual glands, may result in the abnormal growth of hair, marked physical development and the premature development of secondary sexual characteristics, other symptoms produced by hypertrophy of the suprarenal cortex

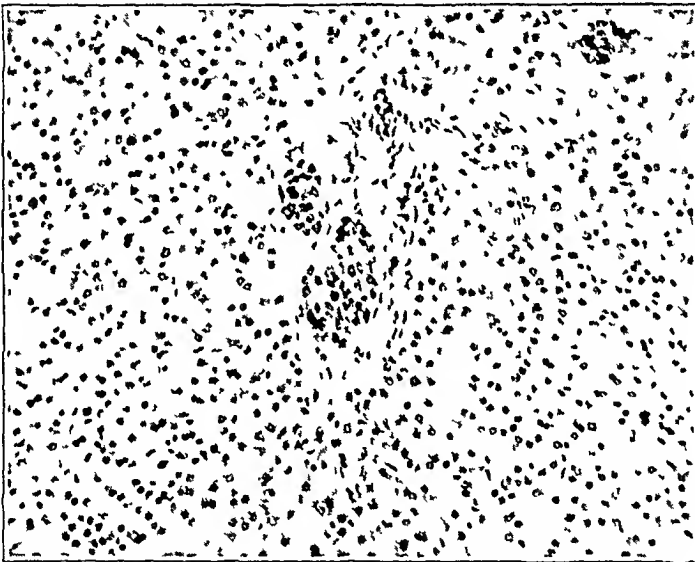


Fig 5—Microscopic section showing metastasis to the liver and periportal spaces

serve to differentiate the “syndrome génito-suprénal” from other causes of hypertrichosis and virilism.

The sexual alterations produced by hypertrophy of the suprarenal cortex are always in the direction of masculinization—toward the adult male type. Thus, the young female becomes pseudohermaphroditic, with an enlargement of the clitoris, an early growth of pubic hair and a tendency for its distribution to assume the masculine type. The young male exhibits precocious puberty, with sexual precocity. No evidence

3 Hoskins, R. G. Hypergenitalism and Hypogenitalism, in Abt, I. A. Pediatrics, Philadelphia, W. B. Saunders Company, 1924, p. 745.

4 Quinby, W. C. A Case of Pseudo-Hermaphroditism, with Remarks on Abnormal Function of the Endocrine Glands, Bull. Johns Hopkins Hosp. **27** 50, 1916.

has been found, however, to indicate an increase in spermatogenesis, rather, the reverse seems to be true. The type of sexual alteration produced by hypertrophy in early adult life is well illustrated by our case and by that described by Gordon Holmes⁵. His case was that of a large, slowly growing tumor of the right suprarenal cortex in a young woman. The tendencies toward the loss of feminine sexual characteristics with a change toward masculinization were exhibited as follows: (1) alterations in the sexual organs, with atrophy of the uterus and overgrowth of the clitoris, (2) disturbance of the sexual functions, especially amenorrhea, (3) changes in the secondary sexual characteristics, with an abnormal growth of hair, atrophy of the breasts, alterations

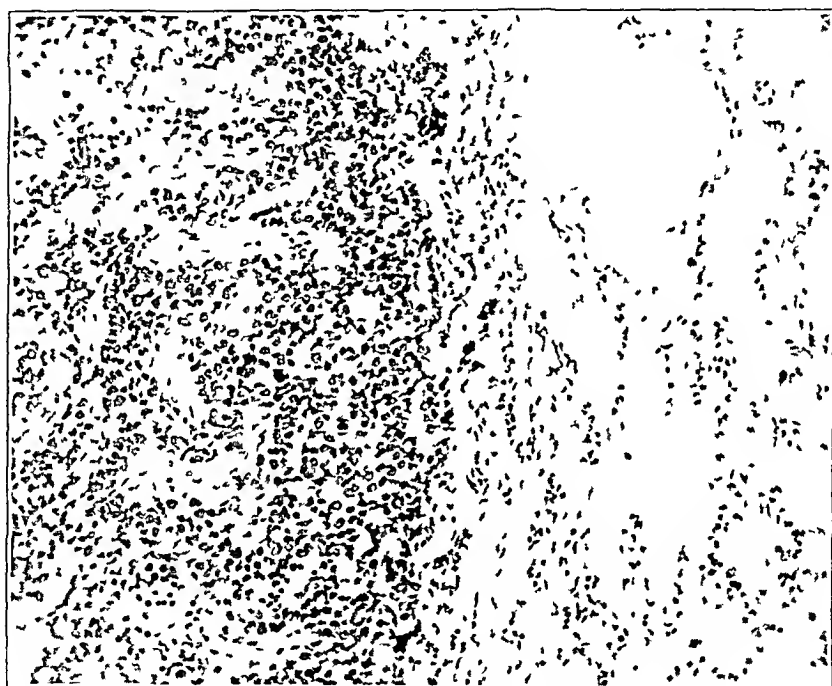


Fig. 6—Microscopic section showing metastasis to the lung

in the distribution of fat and the development of masculine limbs, and (4) psychic changes, with loss of erotic feelings and lack of modesty.

An important observation in the genito-suprarenal syndrome is the presence of hypertension. Oppenheimer and Fishberg⁶ called particular attention to this symptom in association with suprarenal tumors. It will be noted that on admission to the hospital our patient, a girl of 13, had a blood pressure of 158 systolic and 85 diastolic, with no evidence

5 Holmes, Gordon. A Case of Virilism Associated with a Suprarenal Tumor. Recovery After Its Removal, *Quart J Med* **18** 143, 1924-1925.

6 Oppenheimer, B. S., and Fishberg, A. M. The Association of Hypertension with Suprarenal Tumors, *Arch Int Med* **34** 631 (Nov.) 1924.

of nephritis. The reason for the production of hypertension is obscure, for Tokumitsu⁷ has shown that the injection of suprarenal cortex into animals, unlike the effect of medullary extract, causes a drop in the blood pressure.

Pigmentation is frequently found associated with tumors of the suprarenal cortex. It differs in distribution from that found in Addison's disease, and is not a constant observation. Rough skin and an acneiform eruption, especially over the trunk and face, are also fairly frequent symptoms. Attention was called to this condition by Jump, Beates and Babcock,⁸ who analyzed 18 cases of tumor of the suprarenal cortex in

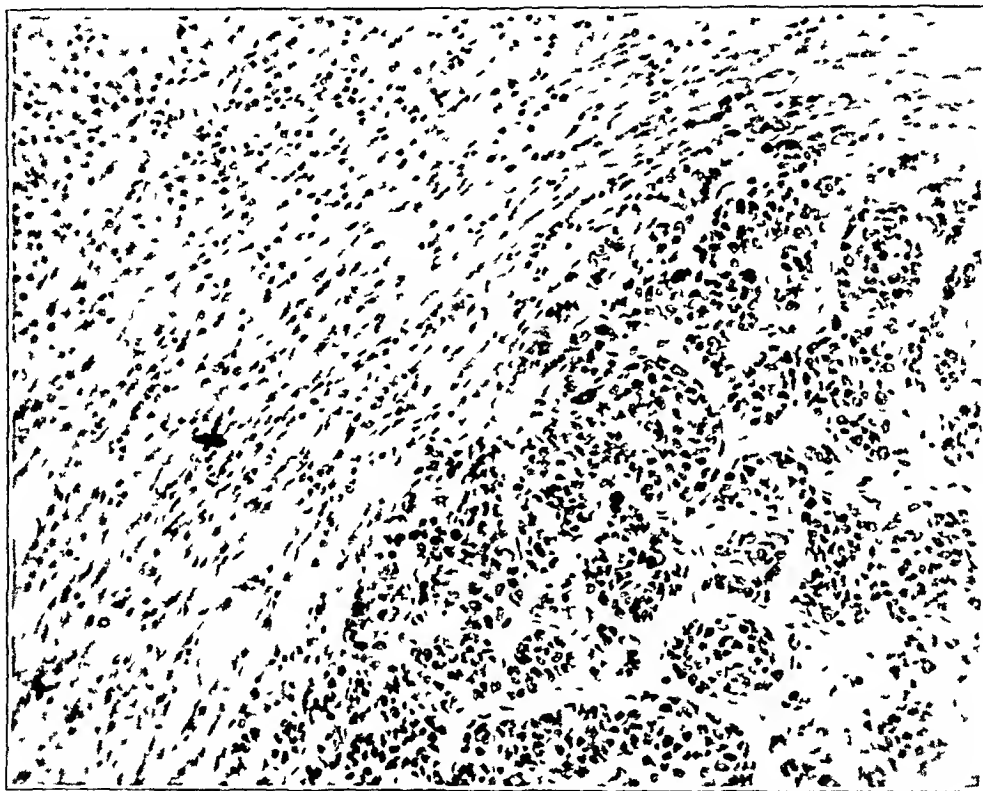


Fig 7—Microscopic section showing metastasis to the liver

1914. It was present in our case. Some patients display mental precocity. The majority are, however, mentally dull, with a diminution, particularly in females, in what would appear to be an instinctive sense of modesty. Riesman⁹ called attention to the occasional occurrence of gastric dis-

7 Tokumitsu, Y. On the Function of the Suprarenal Cortex and Its Relation with Other Endocrine Glands, *Japan M. World* 3:212, 1923.

8 Jump, H. D., Beates, N., and Babcock, W. W. Precocious Development of the External Genitals Due to Hypernephroma of the Adrenal Cortex, *Am. J. M. Sc.* 147:568, 1914.

9 Riesman, D. Diseases of the Adrenal Glands, in Christian, H. A., and Mackenzie, J. *The Oxford Medicine*, New York, Oxford University Press, 1920, vol. 3, p. 791.

orders and vomiting, even in the absence of metastatic causes for such complaints. Finally, there is a variety of symptoms which may result from metastatic growths in the kidneys, liver, brain, lungs, etc., and which obviously vary greatly in individual patients.

Experimentation on animals has resulted in the accumulation of a few facts concerning hyperfunction of the suprarenal cortex. Thus, Stilling¹⁰ has shown that the adrenals are enlarged in male rabbits during breeding. Gueysse¹¹ found enlargement of the adrenal glands in pregnant guinea-pigs. Schenk¹² and Cecca¹³ found an increased amount of cortex in castrated rabbits—a condition that they took to be compensatory. In studying the cause of retarded sexual development in certain persons, Karakascheff¹⁴ constantly found an atrophy of the suprarenal glands. Berner¹⁵ described a hen which had spurs and a comb, never laid eggs and had the strutting gait of a cock, but which never crowed. It was found to have a tumor of the right adrenal cortex with metastases to the peritoneum, lungs and ovary. Fordyce and Evans¹⁶ stated that sexual changes of two types occur, depending on whether the tumor is in a male or a female. If in the latter, all changes in the secondary sexual characteristics tend toward masculinization, whereas in the former, an intensification of male characteristics occurs, but with no increase of potency. Lack of spermatogenesis in such cases has been noted by Fordyce and Evans, Adams,¹⁷ Guthrie and Emery¹⁸ and Tschernobrow.¹⁹

10 Stilling, H. Zur Anatomie der Nebennieren, Arch f mikr Anat **52** 176, 1898.

11 Gueysse, A. La capsule surrenale du cobaye, J de l'anat et de la physiol **37** 312, 1901.

12 Schenk, F. Ueber die Veränderungen der Nebennieren nach Kastration, Beitr z klin Chir **67** 316, 1910.

13 Cecca, M. Glandes à secretion interne etudiees au point de vue chirurgical, Presse med **12** 301, 1904.

14 Karakascheff, K. I. Beiträge zur pathologischen Anatomie der Nebennieren. Atrophie, vikarierende hypertrophie, Tuberkulose, Beitr z path Anat u z allg Path **36** 401, 1904.

15 Berner, O. Suprarenal Virilism, Norsk mag f lægevidensk **84** 849 (Oct) 1923.

16 Fordyce, A. D., and Evans, W. H. Suprarenal Virilism, Quart J Med **22** 557 (July) 1929.

17 Adams, Charles. A Case of Precocious Development Associated with a Tumor of the Left Adrenal Body, Tr Path Soc London **56** 208, 1905.

18 Guthrie, L., and Emery, W. D'Este. Precocious Obesity, Premature Sexual and Physical Development and Hirsuties in Relation to Hypernephroma and Other Morbid Conditions, Tr Clin Soc London **40** 175, 1907.

19 Tschernobrow, E. Ueber eine Geschwulst der Nebennieren bei einem 11 jährigen Knaben mit früh-zeitigen Geschlechtsentwicklung, Thesis, Zurich, 1919.

Various theories have been proposed to account for the secondary sexual manifestations accompanying suprarenal tumor 1 Bulloch and Sequeira,²⁰ Glynn²¹ and others expressed the opinion that tumor of the cortex results in accentuation of the normal physiologic function of that portion of the organ 2 Gallais¹ expressed the belief that the sexual changes result from a pluriglandular disturbance, with hyperfunction of the cortex affecting the ovary in the female 3 Blanchard²² believed the cause to lie exclusively in disturbances of the sexual glands 4 Krabbe²³ believed that the tendency toward masculinization occurs in both sexes because the tumor develops from sexual glands of the masculine type, which, early in the embryo, become involved in the suprarenal cortex

PATHOLOGY OF TUMORS OF THE SUPRARENAL GLAND

Ewing²⁴ gave the following classification of tumors of the suprarenal gland

Medullary

- (a) Focal hyperplasia of
 - (1) Glial tissue or
 - (2) Chromaffin cells
- (b) Neuroma ganglionare
- (c) Neurocytoma, "sarcoma"
- (d) Suprarenal chromatophoroma

Cortical

- (a) Hyperplasia, nodular or diffuse
- (b) Adenoma
- (c) Carcinoma

Of the medullary types, the neurocytoma has attracted most attention, as it has been observed more frequently than the other types, and because of its probable identity with congenital sarcomas and lymphosarcomas of the suprarenal gland as well as with retroperitoneal round cell sarcomas in infants and many embryonal growths of the cervical,

20 Bulloch and Sequeira On the Relation of the Suprarenal Capsules to the Sexual Organs, *Tr Path Soc London* **66** 189, 1905

21 Glynn, E A Comparison Between Ovarian "Hypernephroma" and Luteoma and Suprarenal Hypernephroma, with Comments on Suprarenal Virilism, *J Obst & Gynec Brit Emp* **28** 23, 1921, The Adrenal Cortex, Its Relation to Other Ductless Glands and Especially to Sex, *Quart J Med* **5** 157 (Jan) 1912

22 Blanchard, R Le virilisme et l'inversion des caractères sexuels sont sous la dépendance des glandes génitales interstitielles, *Bull Acad de med, Paris* **76**: 47, 1916

23 Krabbe, K N The Relation Between the Adrenal Cortex and Sexual Development, *New York M J* **114** 4 (July 6) 1921

24 Ewing, James Tumors of the Adrenal, in *Neoplastic Diseases, A Treatise on Tumors*, Philadelphia, W B Saunders Company, 1928, p 811

thoracic and peripheral nervous system. The structure of these tumors varies with the degree of development of the nerve elements. According to Ewing, "the most immature types are perfect rosettes, very numerous, but ill-defined fibrils giving an abundance of hyalin stroma, or many hyalin globules staining with eosin. The hyalin globules resolve themselves into bundles of imperfect nerve fibrillae connecting groups of neurocytes. Various other structures may be interpreted as imperfect ganglion cells, axis cylinder processes, and glial fibers."

There are two well recognized clinical types of suprarenal neurocytoma. Hutchison²⁵ described a suprarenal sarcoma in infants with cranial metastasis. He reported 13 cases occurring in children from 3 months to 9 years of age. The metastasis may appear spontaneously or following trauma, with ecchymosis of the eyelids, soon followed by exophthalmos and a tumor of the orbit and temporal regions, with extensions to the regional lymph nodes. The orbital tumor may reach a large size, the primary abdominal focus being discovered only at autopsy. Other tumors besides those arising in the suprarenal gland may, of course, produce the same syndrome.

The second type is that described by Pepper²⁶ in which the prominence of hepatic metastases produces the striking clinical feature, with a rapidly enlarging abdominal tumor caused by growths in the suprarenal gland and liver. Frew²⁷ has shown by anatomic studies of lymphatic drainage why it is that tumors of the left suprarenal gland usually produce Hutchison's type of picture, whereas tumors of the right suprarenal gland follow the picture described by Pepper.

Vaquez²⁸ and others have noted high arterial tension with tumors of the suprarenal medulla, and epinephrine-like substances have been extracted from medullary tumors.

TUMORS OF THE CORTEX

The simplest change in the cortex with neoplastic tendencies is hyperplasia. The hyperplasia may be nodular or diffuse. Both types are relatively rare. In the nodular form light yellow masses are seen, which vary in size from 1 mm to 1 cm in diameter. Diffuse hyperplasia may produce a syndrome of feminine pseudohermaphroditism.

25 Hutchison, R. On Suprarenal Sarcoma in Children with Metastases in the Skull, *Quart J Med* **1** 33, 1907-1908.

26 Pepper, W. A Study of Congenital Sarcoma of the Liver and Adrenal, with Report of a Case, *Am J M Sc* **121** 287, 1901.

27 Frew, R. S. On Carcinoma Originating in the Suprarenal Medulla in Children, *Quart J Med* **4** 123 1910.

28 Vaquez, H. Hypertension, *Bull et mem Soc med d hôp de Paris* **21** 120, 1904.

In structure, the areas of hyperplasia may resemble the normal zona glomerulosa or zona reticularis

Adenoma of the suprarenal cortex is also infrequently encountered Ewing found only 3 instances in a series of 1,500 autopsies They may reach a large size, and the cells composing the adenoma may closely resemble those of the normal suprarenal cortex More often they are smaller, more granular and free from fat

Carcinoma of the suprarenal cortex may occur at any age, though in a series of 9 collected cases Rolleston and Marks²⁹ found the average age to be 44 years The tumors, grossly, are soft and yellowish, with a marked tendency toward hemorrhage and necrosis They are solid, though central softening may lend them a pseudocystic structure Characteristics are the early and widespread metastases to distant organs, local extension to the kidneys and perirenal tissue and the infrequency of metastases to the bone

Ewing described two forms of carcinoma of the suprarenal cortex

1 Adenocarcinoma, or adenoma malignum, resembles the adenoma described, with an orderly arrangement of cells reproducing the alveoli of the zona glomerulosa, or the anastomosing columns of the zona fasciculata There are in addition, however, typical areas of a malignant character, and the tumor metastasizes No diffuse growth of typical cells occurs The atypical cells are large and the nuclei hyperchromatic

2 Fully developed carcinoma presents several peculiarities of structure There are numerous areas of large, granular, fatty cells in perivascular arrangement, resembling vascular adenocarcinoma The cells are, however, more active, atypical and malignant Giant cells are seen in varying proportions In some tumors almost the entire growth seems composed of the giant cells A type described by Ewing as carcinosarcoma consists of areas of alveolar or perivascular carcinomatous types of arrangement, interspersed with other areas in which are seen sheets of elongated, spindle-shaped, granular cells Diffuse carcinoma is the most malignant form Here the cells lose their resemblance to suprarenal parenchyma, and appear as rounded or polyhedral granular cells, notably free from fats and glycogen They infiltrate surrounding tissues and produce bulky metastases

Incidence of Tumors of the Suprarenal Cortex—Carcinoma of the suprarenal cortex is a relatively infrequent form of tumor In 1897, Williams³⁰ reported a single case in 8,378 tumors found in infants

29 Rolleston, H D, and Marks, H W J Primary Malignant Disease of the Suprarenal Bodies, *Am J M Sc* **116** 383, 1898

30 Williams, R The Malignant Tumors of Infancy, Childhood, and Youth, *Lancet* **1** 126, 1897

and children In 1899, Ramsay³¹ was able to collect 57 cases of primary malignant tumors of the suprarenal gland as a whole, including medullary tumors In the literature Gallais¹ found 51 cortical tumors with sexual alterations, all occurring in women and children In analyzing 47,069 cases at the University of California Hospital, Gibson³² found a total of 9 tumors of the suprarenal gland Of these, only 4 proved to be primary suprarenal tumors, 2 being cortical and 1 medullary

In 1925, Apert² was able to collect only 35 cases of cortical suprarenal tumor in which necropsy had been performed In 1905, Bulloch and Sequeira²⁰ collected 12 cases of tumor of the suprarenal gland with sexual alterations In 1928, Crosbie and Smith³³ described what they believed to be the nineteenth case of cortical suprarenal tumor, with typical changes in secondary sexual characteristics Recently (1929), Fordyce and Evans¹⁶ contributed 2 more cases of suprarenal virilism, one resulting from a carcinoma of the suprarenal cortex, the other from an operable, encapsulated tumor of the suprarenal cortex

Though we made no attempt to collect every case that has been reported, we feel that the incidence of suprarenal tumors is sufficiently infrequent to justify the report of our case

The Relation of Cortical Suprarenal Tumors to Renal Hypernephromas—A review of the subject of suprarenal tumors would be incomplete without some mention of the present status of the relationship between suprarenal tumors and so-called renal hypernephromas

The well known Grawitzian theory,³⁴ propounded in 1883, ascribes the occurrence of hypernephromas of the kidney to rests from the suprarenal cortex This theory is supported by the embryonal proximity of the suprarenal cortex to the renal anlage and by the gross resemblance of hypernephromas to suprarenal carcinomas Present opinion, however, is not in accord with Grawitz' theory Glynn²¹ excellently pointed out differences in the microscopic structure of the two tumors, and called attention to the fact that there is no association of renal hypernephroma with changes in sexual characteristics A possible exception to this statement is found in the case reported by Richards,³⁵ in which, however, the growth in the kidney was bilateral

31 Ramsay, O A Study of Fifty-Seven Cases of Primary Malignant Tumors of the Suprarenal Glands, *Bull Johns Hopkins Hosp* 10 20, 1899

32 Gibson, T E Diagnosis of Adrenal Tumors, with Classification of Adrenal Tumor Syndromes, and Report of Cases, *J Urol* 18 33 (July) 1927

33 Crosbie, A H, and Smith, L W Primary Tumors of Suprarenal Capsule with Especial Reference to Adrenal Virilism, *Tr Am A Genito-Urin Surgeons* 20 179, 1927

34 Grawitz, P Ueber Entwicklung der Nierentumoren, *Deutsche med Wchnschr* 10 719, 1884

35 Richards, Owen Growths of the Kidney and Adrenals, *Guy's Hosp Rep* 59 217, 1904

and might well have been metastatic from an unrecognized primary focus in the suprarenal gland. Supporters of the Grawitzian hypothesis have yet to explain why suprarenal rests, though comparatively uncommon in the kidney, produce such a common tumor as hypernephroma—by far the commonest renal tumor—while suprarenal rests in other organs, though common, rarely produce tumors, benign or malignant. In 1,500 autopsies reviewed by Glynn, only 2 cases of nodules resembling suprarenal rests were found in the kidneys, both of these being papillary cystadenomas. Kelly³⁶ and Manasse³⁷ in their large series of autopsies did not give a single example of renal suprarenal rests.

As opposed to the infrequency of suprarenal rests in the kidney, the following data are illustrative of the comparative frequency of suprarenal rests in other organs. Wiesel³⁸ found suprarenal rests in the epididymis in 76 per cent of new-born males. Schmorl³⁹ found suprarenal rests in 4 of 510 livers examined at autopsy. Aichel⁴⁰ found rests in the broad ligaments and spermatic veins of twenty-four females. In these rests hyperplasia and adenoma is an extremely rare occurrence, and in 5 cases of Grawitzian tumors of the ovary reported by Vouviller,⁴¹ none exhibited unusual sexual changes, all resembling renal hypernephromas rather than suprarenal carcinomas.

This evidence, though not conclusive, points strongly to the fact that renal hypernephroma bears no more than an accidental structural relationship to suprarenal carcinoma.

PROGNOSIS AND TREATMENT

The prognosis of tumors of the suprarenal depends, as does that of neoplasms elsewhere in the body, on the character of the growth, the degree to which it has infiltrated adjacent structures and the extensiveness and accessibility of its metastases. Gibson³² pointed to pyelography as a method of recognition of suprarenal tumor or confirmation

36 Kelly, A. Ueber Hypernephrome der Niere, Beitr z path Anat u z allg Path **23** 280, 1898.

37 Manasse, Paul. Ueber die hyperplastischen Tumoren der Nebennieren, Virchows Arch f path Anat **133** 311, 1893.

38 Wiesel, Josef. Accessorische Nebennieren im Bereiche des Nebenbodens, Wien klin Wchnschr **11** 443, 1898.

39 Schmorl, Georg. Zur Kenntnis der accessorischen Nebennieren, Beitr z path Anat u z allg Path **9** 523, 1891.

40 Aichel, Otto. Zur Kenntnis der Nebennieren, Munchen med Wchnschr **47** 1228, 1900.

41 Vouviller, Paul. Grawitz'sche Nebennieren Geschwulst des Ovariums, Beitr z path Anat u z allg Path **50** 161, 1911.

of its diagnosis. He called attention to the fact that the upper calices are compressed and the entire kidney pushed downward.

In at least 3 cases, successful removal of the tumor has been effected, with complete reversion of sexual characteristics to normal. Mauclaire,⁴² Collett⁴³ and Holmes⁶ reported cases in which operation had been successful. Holmes' patient was a young woman, with a large, slowly growing neoplasm of the right suprarenal cortex which Glynn, who examined it, believed to be benign. Collett's case was that of a girl 1½ years of age, and is probably the only one on record of the removal of an unquestionably malignant tumor of the suprarenal cortex with complete recovery. Crosbie and Smith³³ recently reported a case in a woman, 38 years of age, in whom a cortical suprarenal adenoma with cystic degeneration and hemorrhage was removed, with apparent reversion of the secondary sexual changes, consisting of enlargement of the clitoris and hirsutism.

55 East Washington Street

42 Mauclaire, P. Tumeur de la conche corticale de la capsule surrenale droite observee chez une femme et ayant provoque l'habitus masculin, Bull et mem Soc de chir de Paris **46** 796, 1920.

43 Collett, Arthur. Genito-Suprarenal Syndrome (Suprarenal Virilism) in a Girl One and a Half Years Old, with Successful Operation, Am J Dis Child **27** 204 (March) 1924.

TUMORS OF THE HEART AND PERICARDIUM

PATHOLOGY, SYMPTOMATOLOGY AND REPORT OF NINE CASES *

WALLACE M YATER, M D

WASHINGTON, D C

Tumors of the heart and pericardium, both primary and secondary, are rare. Most of them are asymptomatic and are, therefore, of interest only to the pathologist. Some, however, are the cause of cardiac dysfunction or even failure, and are thus of some concern to the clinician. Only once has a primary tumor of the heart been diagnosed during life and only a few times, a metastatic lesion. A review of the clinical history of some of the cases on record shows that occasionally a neoplasm might have been suspected had the clinician borne this possibility in mind. There is something intensely satisfying in diagnosing correctly a rare lesion, and it is hoped that this article will impress its readers so that they will be on the alert to recognize the condition should it happen to come under their observation. I shall attempt a comprehensive but not complete review of the subject and shall add several cases to the literature.

SECONDARY TUMORS OF THE HEART

Secondary tumors of the heart are perhaps somewhat less rare than the primary neoplasms. There are four interesting questions that might be asked that apply to metastatic growths in the heart, two of which (1 and 4) are applicable also to certain types of primary growths. 1 Why are neoplasms so uncommon in the heart? 2 Why do metastatic lesions have such a predilection for the right side of the heart? 3 Why are the valves practically never involved in secondary growths? 4 Why do such massive growths occur with extensive destruction and replacement of myocardium or with mechanical embarrassment, and yet produce in many instances so little disturbance of cardiac function?

As regards the first question, the heart is probably unfavorable for implantation because of its active contraction (Jagers). Adam¹ said

The heart above all organs is constantly in a state of great efficiency, well nourished, well innervated and functionally always active, so that it is less likely to take on aberrant growth.

Karrenstein gave the incidence of cardiac metastases as 7.5 per cent in cases of disseminated growths. He cited the following statistics

* Submitted for publication, Jan. 12, 1931.

¹ From the Georgetown University School of Medicine.

In 2,161 autopsies, Chambers found 7 secondary carcinomas of the heart, from 4,547 autopsies, Willigk reported 9 secondary carcinomas of the heart, 7 of which were in the pericardium, in 4,500 autopsies, Uskoff found 1 secondary carcinoma of the heart, in about 8,500 autopsies, Napp saw 3 secondary carcinomas of the heart, at the Roth Institute of the University of Berlin (Karrenstein), among 6,655 autopsies there were 15 carcinomas (8 of which were pericardial) and 4 secondary sarcomas of the pericardium. Peters and Milne gave more statistics. Blumensohn reported that of 1,078 cases of disseminated carcinoma, the heart was involved in 34, and of 160 cases of sarcoma, in 12. Pic and Bret found 25 metastatic carcinomas of the heart in 1,708 autopsies, Thorel found 15 in 3,000 autopsies, and Ely 7 in 2,161 autopsies. At the Russell Sage Institute of New York there were 3 cancers of the heart in 1,976 autopsies, at the Johns Hopkins Hospital up to the year of 1907, there were 10 tumors of the heart in 2,942 autopsies, all secondary except a rhabdomyoma. At the Stanford Medical School, Morris reported 2 carcinomas and 3 sarcomas in 3,000 autopsies.

Metastases to the heart have occurred from neoplasms of all of the main organs

Cancer of the trachea (Linell)

Cancer of the tongue (Lisa) (Geipel)

Cancer of the stomach (Peters and Milne) (Widal and Abram) (Geipel) (Moore)

Sarcoma of the kidney (Moore) (Rabe and Morel)

Cancer of the submaxillary gland (Wagner)

Rodent ulcer of the face (Pic and Bret)

Cancer of the esophagus (Moore) (Geipel, six cases)

Cancer of the rectum (Peters and Milne) (Thorel)

Lymphosarcoma (Peters and Milne) (Aubertin) (Morris) (Windholz) (Napp)

Cancer of the pancreas (Barthelemy)

Cancer of the breast (Hektoen) (Kapsinow) (Goldstein) (Ehrenberg) (Geipel)

Sarcoma of bone (Hektoen) (Goldstein) (Allyn and Karsner) (Morris) (Laplace and Karsner) (Tedeschi) (Bardenheuer) (Willius and Amberg)

Sarcoma of the eye (Goldstein)

Pigmented soft mole of labium majus (Goldstein)

Cancer of the uterus (Geipel, two cases) (Rist and Rolland) (Thorel, two cases)

Cancer of the lung (Caussade, Surmont and Lacapere) (Bosco) (Morris) (Windholz)

Cancer of the testis (Kanthack)

Hypernephroma (Patzdorf) (Polaves and Taft)

Sarcoma of the skin (Allyn and Karsner)

Sarcoma of the pleura (Pommay-Michaux and Boue)

Sarcoma of the nose (Warthin)

Cancer of the bronchus (Geipel) (Morris) (Fishberg, two cases)

Cancer of the clitoris (Arnold)
Sarcoma of the uterus (Thorel)
Cancer of the gallbladder (Thorel)
Cancer of the kidney (Thorel)
Cancer of the vulva (Geipel)
Cancer of the ovary (Geipel)
Cancer of the liver (Geipel)
Epidermoid carcinoma of the scalp (Campagna, Maurice and Hauser)
Metastases to the heart from a primary tumor of the heart itself, usually sarcoma, also occur

There are three types of secondary invasion of the heart. Secondary invasion occurs most commonly as part of general dissemination, next in order of frequency, as a more or less solitary metastasis from a nearby organ and least often by direct extension from an adjacent organ.

In the majority of cases in which metastasis has occurred, the transmission has been considered as having been made through the blood. Tumor cells have been found in circulating blood, in thrombi (Peters and Milne, and Menetrier), as vegetations on the endocardium and as strands of cells loose in the coronary vessels (Moore), huge masses of tumor tissue have been found filling the venae cavae and the right side of the heart, as in the case of Carnot and Lambling of sarcoma of the stomach and as in case 4 of this report of hypernephroma. Many cases are associated with primary or secondary intrathoracic neoplasms, from which the tumor cells may gain access to the left side of the heart through the pulmonary veins and thence to the coronary arteries and the cardiac muscle. In the less common cases of implantations on the endocardium of the right side of the heart, the tumor cells probably gain entrance to the blood stream from the lymphatic duct, and pass to the superior vena cava via the bronchial and azygos veins (Hektoen). From these grafts it may even be possible that emboli pass into the lungs and cause metastatic lesions there (cases of Delherm and Laignel-Lavastine, Rist and Rolland, and Warthin).

Probably a smaller number of metastases occur through the lymphatics. This would come about by retrograde conduction through the tracheobronchial lymph nodes, which drain the myocardium and pericardium as well as the pleura and lungs (cases of Aubertin and of Wolf and Giet).

In case of direct extension, the lymphatic canals may or may not play an important rôle. Strands of tumor cells invade the interstices of the surrounding tissues and by their mass destroy by pressure, or they follow fascial planes in the lines of least resistance. This mechanism is, of course, possible with primary tumors of the lung, bronchi, esophagus or mediastinum or from secondary involvement of intrathoracic lymph nodes. Two of Geipel's cases demonstrate different

modes of direct extension In one, a carcinoma of the bronchi broke through into the upper left pulmonary vein and extended into the left auricle, while in the other a carcinoma of the esophagus forced itself through the wall of the left auricle In one of Napp's cases, a medullary sarcoma of the posterior mediastinum grew into the muscle of the heart through the right auricle, in another, the left auricle was invaded, while in a third, not only was the right auricle invaded from above but metastatic nodules were found in the wall of the right ventricle In a case reported by Morison a mediastinal sarcoma almost completely replaced the walls of both auricles and of the right ventricle and the apex of the left ventricle

As to the types of secondary lesions and their size, shape and distribution there is the greatest variation Carcinomatous metastases are more common than sarcomatous The lesions are frequently similar to those found in other organs, viz, small, whitish, firm nodules, discretely or diffusely scattered throughout the myocardium In other cases, more often of sarcoma, there may be a diffuse infiltration and replacement of the myocardium, sometimes with great thickening of the walls and encroachment on the cavity (case of Windholz) The nodules may be of large size and project internally, externally or both The heart may or may not be enlarged and deformed, depending on the extent and nature of the involvement The valves are rarely involved, although in the cases of Widal and Abram, Rist and Rolland, and Kanthack large vegetations occurred from tumor cells engrafted on the valves, and the condition resembled vegetative endocarditis Occasionally a large polypoid growth encroaches on the chamber of the heart (Pommay-Michaux and Boué), this may be pedunculated In Waithin's case a metastatic nodule lay free in the cardiac cavity and acted as a ball valve The secondary growth may rarely outstrip the primary growth The pericardium may be involved by an infiltration, with thickening, often in such cases there is a fibrinous exudate on the two layers and a hemorrhagic or nonhemorrhagic effusion In rare cases the superficial lymph vessels of the heart and pericardium are involved in a carcinomatous lymphangitis and stand out as whitish threads (Aubertin) The histologic structure of the primary tumor is usually reproduced With the sarcomas there is often an infiltration of cells between the muscle fibers of the myocardium, causing atrophy of the fibers Leukemic infiltrations may produce, besides diffuse infiltrations, definite nodules resembling tumor metastases (Cochineal and Jolly) (Willius and Amberg) Similarly, animal parasites such as *Cysticercus*, may cause tumor-like nodules in the heart, *echinococcus* cysts and *hydatids* (Monckeberg)

The location of the lesions may be anywhere, but the right side of the heart, especially the ventricle, seems to be favored. The lesions are intramural, subendocardial, subepicardial, septal, auricular, ventricular, etc. The orifices are seldom encroached on to a serious extent. Involvement of the conduction system may produce heart block.

Why the right side of the heart should be more commonly or more extensively involved than the left is rather well explained, as Windholz pointed out, by the work of Kretz. Since studies of the lymphatic system do not seem to explain the predilection, Kretz, using the method of Crănișanu, injected a solution through the coronary arteries constantly for five minutes at a pressure of 130 mm of mercury and measured the fluid escaping from the coronary veins and the cavities of the heart. He found that one fifth of the fluid escaped through the coronary veins while four fifths was lost into the chambers, of the fluid in the chambers, one fourth was lost in the left and three fourths in the right side of the heart. Of the fluid passing out through the coronary veins, one fifth went from the left and four fifths from the right. Kretz explained that the fluid passing directly into the cavities of the heart passed from the coronary arteries to the *venae mininae thebesii*, and by injecting a colored medium he demonstrated this route. Thus the reason for the preference of tumor cells for the right side of the heart may be explained on a blood-vascular basis. The freedom of the valves from involvement, except rarely by implantation, is explicable likewise on a circulatory basis, the valves being relatively avascular.

Concerning the possible reasons for the frequent lack of serious cardiac dysfunction in the presence of extensive neoplastic involvement of the heart, both from primary and secondary growths, Geipel assumed that the slow development of the growth may give time for compensatory changes, while Bardenheuer expressed the opinion that it is due mainly to freedom of the valves from invasion. These reasons hardly seem sufficient when one considers the following cases, in which cardiac symptoms were either lacking or of minor nature or practically terminal in occurrence. Grawitz' case of thymic lymphosarcoma spread into the superior vena cava and formed an envelope about the left auricle from 1 to 2 cm thick, while the entire right ventricle was practically sarcomatous. In Morison's case of mediastinal sarcoma there was practically no ventricular myocardium left. Metastases from a gastric carcinoma so completely involved the heart (Napp) that only a part of the myocardium at the apex was left, and the chamber of the left ventricle was merely a cleft. In Ehrenberg's case a metastatic tumor the size of a fist enveloped the heart, and the left ventricle appeared as a small appendage thereto. Windholz recorded a mediastinal sarcoma

so involving the heart secondarily that only the anterior surface of the left ventricle was free

The symptomatology from a clinical point of view will be considered under a separate heading

PRIMARY TUMORS OF THE HEART

Primary tumors of the heart are more interesting than secondary, and have been the source of much discussion. More than 150 cases have been reported in the literature. There are a number of kinds of primary tumors that occur in the heart: myxoma, sarcoma, rhabdomyoma, fibroma, lipoma, endothelioma, varix, hemangioma, lymphangio-endothelioma and leiomyoma. Most of the tumors described have been benign, about 20 per cent being malignant. Of 143 cases of primary neoplasms of the heart collected by Mendelstamm (1923), 117 were benign and 26 malignant. The benign tumors were mainly myxomas, the malignant, almost entirely sarcomas. Mendelstamm gave their distribution as follows:

	Right Auricle	Right Ventricle	Left Auricle	Left Ventricle	Both Auricles and Auricular Septum	Both Ventricles and Ventricular Septum	Multiple Sites	Valves
Benign	9	8	44	23	6	5	8	17
Malignant	11	1	2	2	2	2	2	4

Of the valvular tumors, the locations were as follows:

	Mitral	Aortic	Tricuspid	Pulmonic
Benign	2	3	5	4
Malignant	1	1	1	1

For sex distribution, Mendelstamm gave:

	Male	Female
Benign	57	33
Malignant	15	8

For age distribution, he divided the cases as follows:

	Up to 20 Yrs	20-40	40-60	Over 60
Benign	31	17	29	21
Malignant	2	9	8	3

MYXOMA

Myxoma is the most debated type of tumor in the heart. Ribbert was inclined to think that most of the tumors described as myxoma or a variety of myxoma are true neoplasms, while others, like Thorel, Stahr, Karrenstein and Husten, expressed the belief that these tumors are thrombi swollen by imbibition of plasma and in various stages of organization. The latter contended that myxomatous changes may

occur in these edematous thrombi. Thus, of 71 cases described in the literature as endocardial myxomas, Husten, in 1923, after critical analysis, accepted only 9 as true myxomas. One could accept by the same standard 5 other cases reviewed by Mendelstamm (Wigand, Meyer, Hlava, Nowicki [2]), making thus only 14 myxomas. Husten admitted that the differentiation was difficult. Ribbert, on the other hand, claimed that there is no difficulty in the distinction. It appears that most men continue to call these questionable formations myxomas. Altogether about 75 cases of myxoma arising from the mural endocardium have been described.

Myxomas range in size upward from that of a pea, often becoming as large as a hen's egg or a medium sized apple. They may be smooth and rounded, lumpy or polypoid and villose. The surface is smooth and glistening, as a rule, and the appearance gelatinous. They are usually pale yellow, bluish gray or yellowish brown, often with hemorrhagic areas on the surface, and sometimes partly covered with fibrin, the consistency is more or less elastic. On cut section they are gelatinous and often hemorrhagic. They are usually attached by a short stalk, and are entirely intracavitary. Microscopically, the tumor is seen to be covered with the normal endothelium of the endocardium. The groundwork is an amorphous, finely granular or finely fibrillar material which may or may not stain as mucin. Cells of different varieties are seen, varying in number in different cases and in different parts of the same tumor, often they are relatively few compared to the amount of tumor tissue. In many there are large stellate cells typical of mucoid tissue. In some there are also cells that are large and multinucleated, others that are fusiform, inflammatory elements, such as lymphocytes and plasma cells, are often seen. Blood vessels are usually present, numerous in some cases, but often scanty, usually of a delicate structure, and appearing as mere capillaries with endothelial walls. Small hemorrhages and scattered erythrocytes are commonly present, together with pigments consisting of hemosiderin and hematoïdin. Connective tissue fibers and often elastic fibers are found. Some of the tumors grossly resemble primary sarcomas of the heart, and really differ essentially only in the predominating type of cell and in their greater cellularity.

Myxomas arise from the endocardium, usually of the chambers and more often of the left auricle in the region of the fossa ovalis, but sometimes from the valves. Most of the small nodules arising from the valves, however, are either greatly modified myxomas or fibromas, endotheliomas, and other tumors.

It seems to me that the argument concerning the nature of these myxomatous masses is all in favor of their neoplastic origin. Ribbert

has been the champion of this view. He maintained that the masses are usually too large to be organized thrombi. Everywhere else in the body thrombi have a tendency to retract and become almost completely effaced. It is difficult to conceive of thrombi forming in otherwise normal hearts not showing the slightest evidence of a previous endocarditis or trauma, as many of the tumors do. These tumors occur almost exclusively in the auricles, whereas thrombi occur just as frequently if not more so in the ventricles. There appears to be an entire absence of stages intermediate between definite thrombi or endocardial vegetations and these myxomatous masses. Ribbert contended that rests of embryonic mucoid tissue in the heart undoubtedly persist at times, especially in the rim of the foramen ovale. Such tumors as these differ from embryonic tissue in that there is a relative increase of mucin. Ribbert explained the fact that the valvular tumors often approach the fibroma because the mucoid tissue originally forming it has become fully formed fibrous tissue, which is the ultimate developmental intention of mucoid tissues. There seems to have been considerable contention concerning the point as to the exclusiveness of mucin in myxomas. Ribbert and Leonhardt maintained that true mucin occurs only in genuine blastomas. Djewitzky, Koniger and Honegger, however, found mucin in undoubted thrombi or thickenings of the endocardium. Too much stress is apparently placed on the presence or absence of mucin. Prolonged fixation in formaldehyde may prevent the staining reaction, or the stains may be untrustworthy. Nowicki considered his case 2 true myxoma, although the mucin reaction to thionin was not obtainable, and star cells were not present. Stahr maintained that myxomas are distinguished from organized thrombi by their poverty of cells. The presence of star cells certainly points toward myxoma, and in true myxomas round and spindle-shaped cells are also observed. The presence of hemorrhages is easily explained by the delicate structure of the vessels and the mechanical conditions to which the tumor is subjected. Lymphocytes and plasma cells always occur in such regions. All tumors may contain hemosiderin. In organized thrombi, hemosiderin is found at the periphery and hematoidin in the center, whereas in these tumors hemosiderin is found scattered throughout. In thrombi, one expects the organization to occur from the periphery and the connective tissue on top of this, but Meioz found a neoformation of capillary vessels in a myxoma in the midst of the fundamental substance in fully organized tissue. One expects stratification in an organized thrombus, but no evidence of stratification is present in these tumors. The presence of elastic fibers is without meaning since they are also present in thrombi, but in these tumors they are more or less peripheral and probably derived from the subendocardium. The presence of elastic tissue has led some observers to give a modified name to the tumor, as Kerrenstein

with his elastomyxoma and Askanazy with his fibro-elastomyxoma. Sometimes the vessels in the tumor show a greater development than is usual in thrombi. Likewise against thrombi is the fact that the vessels and cells of the outer and inner parts are similar. Owing to the vascularity and presence of fibrous tissue, Fabris and Csemes designated their cases as fibro-angiomyxoma. Brenner called his an hemangio-elastomyxoma. The lobulated, villose or aciniform structure of many of the tumors speaks more for the true tumor, but Nowicki did not think that the smooth surface of his two large myxomas was against their neoplastic origin. Finally, as Bohrod pointed out, in spite of the rarity of all tumors of the heart, primary sarcomas originating in the endocardium do occur, and wherever there are malignant mesenchymal tumors, benign tumors may also occur.

Many of these myxomas are unusually interesting because of their size, situation and pedunculated nature which allows them to plug up an orifice of the heart, usually the mitral. The clinical features will be considered later.

FIBROMA

Fibroma is considered next because it is an endocardial tumor and is assumed to be of a similar nature to myxoma. The fibromas arise from the subendothelium of the valves. They are usually single, never larger than a cherry, are papillary and pedunculated. About 25 cases of this type have been reported, all were similar. Nine were located on the tricuspid valve, 6 on the aortic, 5 on the mitral and 5 on the pulmonary. In only 4 cases was there evidence of chronic endocarditis. The cases group themselves into those without and those with an organized system of blood vessels. A few of them closely resemble the mural myxomas previously described, others are similar to the cases reported hereafter by me, avascular, hyaline and sparsely cellular, while others are atypical and difficult to classify, such as the endothelioma of the mitral valve of Forel and the hemangiofibroma of the pulmonary valve of Bohrod. Whether both of these should be grouped here under fibroma is questionable, but they seem to be of the same general nature as the others in this group. At least they are all benign tumors of the cardiac valves.

The main conceptions of the nature of these tumors are that they are all really myxomas, that they are organized thrombi, that they are similar to Lambl's excrescences and that they are connective tissue tumors undergoing various degenerations. Many of the same objections given in the discussion on the myxoma against the thrombus theory of origin apply again, the important ones here being the highly developed papillary nature of the growth, the homogeneous structure and the absence of pigment or other signs found in organizing thrombi. A few

words regarding the theory, first of Koechlin and later of Thorel, that they are similar to Lambl's excrescences might be appropriate. These threadlike processes arising usually on the nodulus arantii or annulus of the aortic valve and rarely from other valves were first described by Lambl in 1856. They are quite common, occurring in about 20 per cent of hearts. They are composed of lamellated hyaline connective tissue with a well defined axis cylinder and are covered by endothelium¹; they are practically without nuclei but have numerous elastic fibers. It seems strange, however, that intermediate forms do not occur and that while the excrescences are common the papillomas are rare, likewise, practically all of Lambl's excrescences are situated, as Dean and Falconer pointed out, on the aortic valve, while only 8 of 27 fibromas (including the cases reported here) were on this valve. When one considers the highly papillary structure, the smooth, shining surface and the fact that the growth occurs usually on a normal valve, the idea of a connective tissue tumor seems logical. If Ribbert's assumption is correct, that mucoid tissue ends developmentally as connective tissue, then one may consider these growths also as myxomas, which some of them closely resemble.

Intramural fibromas, fibroids or chancroids, have been described in earlier years, but it is somewhat questionable if the 2 main cases, those of Luschka and of Albers, were actually of this nature. Monckeberg mentioned a case of fibroma of the ventricular septum described by Wagstaffe. These tumors do not produce clinical symptoms or functional disturbance, all being innocent postmortem discoveries.

SARCOMA

Perlstein, reviewing this type of primary cardiac tumor in 1918 and adding a case of primary sarcoma of the pericardium, found only 31 (including his) recorded cases of primary sarcoma of the pericardium or heart. Since then, at least 15 more have been recorded (Gottel, Goldstein, Godel [2], Rose, Mandelstamm, Pinault, Williams, Kohlenberger, Beck and Thatcher, Nowicki, Matras, Muller, Hill, Diebold)¹. Of 45 of these 46 tumors, 15 were spindle cell sarcoma, 14 round cell (small or medium size), 4 giant cell, 3 myxosarcoma, 3 fibrosarcoma, 4 mixed cell, 1 angiosarcoma and 1 lymphosarcoma. The apparent seat of the original tumor in these cases was

Right auricle	18
Left auricle	9
Pericardium (2 from subepicardial tissues)	10
Right ventricle	2
Right and left auricles	1
Left ventricle and auricle	1
Ventricular septum	1
Aortic valve	1
Pulmonary valve	1
Left ventricle and both auricles	1
Diffuse	1

¹ Not including the "rhabdomyosarcoma" of Bradley and Maxwell

Thus it is seen that the majority of sarcomas of the heart arise from the auricles (preferably the right, and often the interauricular septum) and the pericardium. It is interesting to recall that most of the myxomas arise from the auricles, preferably the left, and often the interauricular septum. Grossly, some of them resemble certain of the sarcomas. Why the malignant growths should preferably arise in the right auricle and the benign in the left is impossible to answer. Metastases occurred in 21 cases as follows

Lung	5
Liver	2
Pancreas	2
Suprarenals	2
Mediastinal lymph nodes	2
Mediastinal lymph nodes and pleura	1
Tracheal lymph nodes and suprarenals	1
Lung and pararenal tissue	1
Lungs, pleura and brain	1
Lungs and pancreas	1
Kidneys	1
Tracheobronchial and mediastinal lymph nodes, pancreas and kidneys	1
Pleura, subcutaneous tissue and peritoneum	1

In 16 cases there was hydrothorax, the fluid being bloody in 6. Pericardial effusion was found in 15 cases, in 10 of which it was bloody. In 7 instances the pericardium was partly or entirely obliterated.

The size of the tumors varies from that of a walnut to that of a child's head. The growth may be intracavitary, intramural, pericardial or mixed. Anatomically, one may also roughly classify the sarcomas into two other groups, those more or less sharply circumscribed and those without sharp limits and rather diffusely involving the heart, sometimes growing over the corona of the heart or invading extensively the mediastinum. Most of the intracavitary tumors fill the auricle in which they have originated. In Baldwin's case a pedunculated tumor, 5 by 6 by 7 cm, lay in the left auricle, being attached by a peduncle to the region of the mouths of the pulmonary veins. In Binder's case a pedunculated tumor the size of a walnut hung down from the right auricle into the mouth of the vena cava, nearly filling the right auricle. Bodenheimer's sarcoma consisted of about twenty nodules on the anterior surface of both auricles, growing into the cavity of the right auricle. In the case of Broadbent, the pericardium was from 0.5 to 1.5 cm thick. In Schoppler's case, the entire pericardium was involved. Crescenti described a sarcoma located intramurally in the ventricular septum in a patient, aged 3 years, who died of scarlet fever. In some cases, as Lambert's, the pericardium was the origin of a growth which extensively infiltrated the myocardium. In Fuhrman's first case, the tumor resembled a bunch of grapes growing on the aortic valve and obliterating the mouth of the right coronary artery, while the left coronary artery was occluded by a plug of tumor tissue (the patient died suddenly without previous symptoms). In Mandelstamm's interesting case, two of the pulmonary valves were involved in two tumor

masses, one the size of a walnut, which almost completely obstructed the mouth of the pulmonary artery, there were large metastatic nodules in both lungs. The tumor in Perlstein's case originated from the subepicardial connective tissue and formed a large intrapericardial cystic tumor on the right, posterior and diaphragmatic surfaces of the heart, measuring 13 by 8 by 5 cm. Redtenbacher's angiosarcoma of the pericardium contained a cavity communicating with the right ventricle. The fibrosarcoma described by Raw had extended continuously from the right auricle through the inferior vena cava to the under surface of the liver. Weiss recorded a tumor the size of a child's head, involving mainly the right auricle, which had broken through the interauricular septum, infiltrated extensively the myocardium and almost completely enveloped the heart. The case of Beck and Thatcher was similar, there were extensive metastases in the pleura, peritoneum and subcutaneous tissue from a sarcomatous thrombus in the left auricle. The case of Williams is unusual in that only the parietal pericardium was involved. From these examples, it is seen that the sarcomas arising in the heart or pericardium are extremely variable in their characteristics and not infrequently malignant.

Sarcomas of the heart may occur at any age, having been found anywhere from the age of 3 to 79 years, most of them coming between 18 and 58 years. They predominate in males, in the proportion of twenty-five to sixteen. The apparent duration of the tumor is from one month to three and one-half years.

Here again, as in secondary tumors, it is difficult sometimes to conceive how the neoplasm can become so extensive and the heart continue to function. In the case of Matras, for instance, one is amazed at the great anatomic involvement of the heart and the brevity of the clinical course and meagerness of the cardiac signs.

The clinical features will be discussed separately.

RHABDOMYOMA

Of all of the primary tumors of the heart the rhabdomyoma is perhaps the most interesting. From the time von Recklinghausen described the first case, in 1863, until Seiffert, in 1900, carefully studied these tumors, there had been much discussion regarding the situation of the large vacuoles seen in the tumor. To the satisfaction of all, Seiffert showed that these vacuoles were within the cell bodies of large embryonic fibers of the cardiac muscle whose sarcoplasmic body had continued to grow without, however, any additional differentiation into the adult type of cell. Normally, these embryonic myocardial fibers develop fibrils at the expense of the vacuoles, so that the fully mature muscle fiber is a solid, compactly fibrillar, cross-striated structure. By means of Best's

carmine Abrischoff demonstrated glycogen granules in the vacuoles of these embryonic muscle fibers. The "spider cells" of earlier writers, originally thought to be connective tissue cells, were shown to be the nuclei of these embryonic muscle fibers suspended in the vacuoles by a network of fibrils from the sarcoplasmic portion of the cell body.

Another thought which had to be exploded was that these large cells, which in many respects resemble Purkinje fibers, were in fact derived from these cells. By showing the absence of any anatomic connection with the elements of the conduction system, Bundschuh, Amersbach and Handorn and others demonstrated conclusively that this theory was wrong. Bundschuh considered that these tumors had already originated in the common mother tissue of the two muscle systems of the heart before their differentiation had occurred, this conception is strengthened by the relatively frequently observed fact that the rhabdomyoma fibers may show a transition into the myocardial fibers at the edges of the tumor.

Much discussion has arisen likewise concerning the nature of these tumors, whether they represent secondary growths from simple rests of embryonic tissue or a generalized disturbance of tissue differentiation. Steinbiss championed the view, based largely on the frequent association of similar malformations in other organs, that these rhabdomyomas are phenomena of a general developmental disturbance due to an abnormal germ condition, and that they have nothing to do with the germ explosions conditioned by mechanical developmental disturbances as conceived by Ribbet. According to Steinbiss, the tumor cells preserve morphologically the embryonal type, but reach a high degree of tissue maturity. This is shown not only by the gigantic size which the tumor cells attain but by regressive changes that are often observed, such as the replacement of connective tissue and sometimes even calcification. All cases appear to have reached their final development in embryonic life, appearing the same whatever the age of the patient. The tumor cells do not increase in number of elements but the single elements may hypertrophy, the sarcolemma increasing to a much greater degree than the myofibrils or contractile elements.

Microscopically then, as indicated, the rhabdomyoma of the heart consists of tubular muscle cells which often have a diameter many times that of normal fibers, where it is thicker and fibrillar, the wall of the tubes shows decided cross striations. In the large central vacuoles or lumens there are nuclei, appearing like spiders in a web, arranged in series at certain distances, and other nuclei are seen in the periphery. In their content of connective tissue, cases differ much, but usually the amount is small. The impression is often given that the tumor elements form a syncytium due to the peripheral fibrils

crossing from one tube to another in the absence either of distinct cell boundaries or uniformity in direction of the long axis, fat is not uncommonly found within the tumor elements. In a case reported by Bundschuh a nodule near the apex of the heart contained both myomatous and lipomatous portions without a sharp line of demarcation. The cases of Tedeschi and Spalty were somewhat similar.

At least 41 cases of rhabdomyoma of the heart have been recorded in man and reports have appeared of instances in the lower animals. The human cases were collected by Farber (1931). In general, there are three morphologic types of rhabdomyoma: (1) solitary, (2) multiple and (3) diffuse. The solitary nodule is usually located at the apex of the heart and is unassociated with other developmental abnormalities. The multiple nodules may be subendocardial, intramural or subepicardial, and may or may not project into the cavities of the heart or the pericardial sac. They show frequent transitions to normal cardiac muscle and are often associated with other developmental conditions, particularly tuberous sclerosis of the brain, mixed cell tumors of the kidneys and adenoma sebaceum of the skin. The patient may or may not be feebleminded or epileptic. In the diffuse variety (cases of Ribbert and Uehlinger), the rhabdomyomatous elements occur as small circumscribed nodules and are also scattered through the cardiac muscle without definite grouping. In Schmincke's case, all of the myocardium was composed of rhabdomyoma fibers, the patient was a new-born infant and the heart was twice normal size but not malformed.

The age incidence of death of persons with rhabdomyoma is: new-born, 4; first year, 14; second year, 5; third year, 5; and 1 each in the fourth, fifth, sixth, seventh, eighth, tenth, fourteenth, sixteenth, twentieth, twenty-first, thirty-first, and thirty-fifth years. Whether death occurs because of the rhabdomyoma depends, of course, on the extent of involvement of the heart, the size of the nodules and the position of large nodules. In the patients of Steinbiss dying at 21 and 35 years of age there were only one or two small nodules and no circulatory embarrassment. When the growth is large and at the apex, in the left ventricle or septum, or obstructing an orifice, such as the pulmonary in Ponick's case, death occurs early. Strangely, in Uehlinger's case of diffuse involvement there was no circulatory embarrassment, the patient dying of tetanus at the age of 20 years.

MISCELLANEOUS TUMORS

Other primary tumors of the heart have been recorded but are rare even compared to those already described. These are the lipoma, lymphangio-endothelioma, hemangio-endothelioma, leiomyoma and rhabdomyosarcoma.

According to Martin, about 21 cases of lipoma have been recorded. The summary of Verhac and Moiel, in 1909, gave 11 previously reported cases, to which they added 1. Besides 4 other possible cases concerning which Verhac and Moiel could not obtain accurate data, Monckeberg mentioned 3 more by Handfoit and another by Dittrich. Thorel claimed 1 for Kirch-Heitel and 1 for Pommei, and Martin described a further case. The lipomas are usually small but may become as large as a hen's egg. They are often subepicardial or subendocardial, but may be intramural. Those that are subepicardial are rather large, flat, smooth, whitish yellow and usually pedunculated. Those that are subendocardial are not as large and are usually sessile. In the case reported by Brewis, the tumor was attached by a pedicle on the interventricular septum, and completely obstructed the tricuspid orifice. In the cases reported by Spalty and Tedeschi, the lipoma was surrounded and penetrated by cardiac muscle fibers. Most of the patients were past middle age and did not have symptoms of cardiac dysfunction. Concerning the origin of the subendocardial lipomas, Thorel asserted that they are derived from those little, usually circumscribed, round or oval clusters of fatty tissue that are seen occasionally under the endocardium of the free wall of the right ventricle or of the septum and rarely of the left ventricle.

To my knowledge, only 3 instances of lymphangio-endothelioma have been described, 2 of which were extremely interesting because they caused complete heart block. The case reported by Armstrong and Monckeberg (1911) was a small tumor, 8 by 6 by 5 mm, located in the region where the bundle of His emerges from the auriculoventricular node, it was interpreted as being derived from the lymph vessels of the node, with which it is richly supplied. This was stated to be the first blastomatous new growth of the specific muscle system reported in the literature. In the case of Lloyd (1929) the tumor was 15 by 12 by 8 mm, without a definite boundary, although quite sharply localized, situated in the region of the auriculoventricular node. The third case was recorded by Forel as a small discoid excrescence with smooth surface and soft consistency, about 2.5 mm in diameter, with a pedicle, located on the auricular aspect of the posterior flap of the mitral valve.

A hemangio-endothelioma was described by Penneman on the anterior wall of the left auricle, about the size of a chestnut and projecting 1.5 cm into the cavity of the auricle. A hemangioma cavernosum was described by Schuster on a papillary muscle of the right ventricle. This is similar to Rau's case of a cherry-sized cavernoma in the subendocardium of the right auricle and to Tian's, of a tumor the

size of a hazelnut in the ventricular septum. Monckeberg expressed the belief that tumors of the type of the latter three were not blastomas, but probably varices.

A malignant leiomyoma was described by Eschbach (1928) as originating from the wall of the pulmonary artery, involving the pulmonary valves and almost completely occluding the left pulmonary artery. There is some question as to the nature of this tumor, possibly it is a polymorphous cell sarcoma or a malignant endothelioma. The author's reasons for his diagnosis seem rather convincing, however. Nagayo described several minute fibromyomatous nodules within a large branch of the left bundle branch.

Bradley and Maxwell (1928) described a large tumor filling the pericardial cavity and invading the cardiac muscle to some extent and with metastases in the lungs, liver and kidneys. Sections showed a polymorphous cell sarcoma with many long spindle cell forms, some of the cells contained faint longitudinal striations. The authors called this a rhabdomyosarcoma.

Primary carcinoma of the heart has never been described, but several rather authentic cases of carcinoma originating in the pericardium have been reported.

VARICES OF THE HEART

Varices, varicose veins, blood nodes or blood cysts are considered because they bear an outward similarity to tumors. In fact, while they are probably due to developmental defects in the new-born or regressive changes in the aged, it is still impossible in certain instances to say positively whether one is dealing with a condition of dilated venous channels or an angioma, as some of these tumors have been called. Husten (1923) collected 31 cases from the literature. The most frequent site for this formation is the rim of the fossa ovalis, especially in the right auricle (23 cases have been reported in the right and 2 in the left auricle). There were 3 instances of varices on the valves, 1 on the pulmonary and 2 on the tricuspid. There were 2 cases of varices on the anterior papillary muscle of the right ventricle and 1 of multiple varices in both ventricles. These varices may be single or occur in small clusters. They may be pedunculated, but are usually sessile and shine through the endocardium as a dark red nodule, rarely larger than a pea. Usually they contain a clot, which may be stratified, and sometimes there is a phlebolith. Some occur in the new-born but most of them are found in adults over 50. According to Nauweick, in the auricle of adults they may represent hypoplasia of the wall of a vein which lies superficially under the endocardium, or they may be

dilated thebesian veins Frank suggested that they are due to congenital narrowness of the mouths of these veins Those on the valves may occur as a failure of regression of the vascular apparatus of fetal life, but Bundschuh, describing one on a pulmonary valve, concluded that the ingoing and outgoing canals open on the surface of the valve Varices are of no clinical importance

PRIMARY TUMORS OF THE PERICARDIUM

All primary tumors of the pericardium are rare Primary sarcoma of the pericardium has been discussed under the heading of primary sarcoma of the heart, when it was said that 10 of 45 sarcomas were of the pericardium Also, when discussing lipoma, it was mentioned that several primary sarcomas had been described on the external surface of the heart, these undoubtedly originated from the small fat lobules which are almost always seen in the connective tissue of the pericardium of fat persons (Thorel) The question has been raised (Stuppeler) whether these represent an embryonal displacement according to the meaning of Ribbert Other types of neoplasm have been recorded Kaufman described lobulated fibrous polyps on the inner surface of a fibrotic, thickened pericardium, the sac of which contained 400 cc of a serosanguinofibrinous exudate Jaisch described a papillary tumor of similar appearance which he concluded was the result of organization of a fibrinous exudate As benign tumors, Oith noted small multiple polypoid tumors of connective tissue containing numerous blood vessels, which may be fibromas or fibrolipomas Hoch described a tumor which, microscopically, was clearly a phlebogenous angioma

Of unusual interest is carcinoma of the pericardium The few cases recorded seem to be instances of endothelial carcinoma derived from the surface cells of the epicardium Dietrich, Garnier, Ceelen, and Broadbent (according to Ceelen's interpretation) each reported a tumor of this type Dietrich's case is rather typical of all A woman, aged 44, presented at autopsy an enormous bulging of the pericardial sac, which contained 1,500 cc of dark red fluid A palm-sized grayish-red, spongy and crumbly, cauliflower-shaped tumor with many small superficial blood vessels covered the collapsed right auricle Microscopically, this tumor was of papillary structure with a connective tissue framework containing large vessels, arising from the parietal pericardium, the framework was filled with clusters of large endothelial-like cells with plump, vesicular nuclei rich in chromatin, and the cells were arranged in concentric layers, but without definite perle formation

A teratoma lying within the pericardial cavity and attached to the root of the pulmonary artery was described by Joel, in 1890

Keller and Callender described a large neurofibroma attached to the parietal pericardium and apparently originating from the phrenic nerve

I have seen a cyst, probably of a lymphatic vessel, 4.5 by 2.5 by 2.5 cm, in the pericardial fat at the apex of the heart

SYMPTOMATOLOGY

Several authors have discussed this subject, particularly Link, Kiehl, Fraenkel, Pavlovsky, Nowicki and Meroz

For convenience of consideration of the symptomatology, I prefer to make the following division, which is quite different from that of previous authors

A Clinical types not suggestive of tumor of the heart

- (1) Absence of symptoms referable to the heart
- (2) Symptoms of cardiac embarrassment terminally
- (3) Symptoms of congestive heart failure
- (4) Sudden death
- (5) Symptoms suggestive of subacute bacterial endocarditis

B Clinical types suggestive of tumor of the heart

- (1) Heart block
- (2) Symptoms referable to location of the tumor other than heart block
- (3) Symptoms of cardiac dysfunction developing without apparent cause in a patient with a known malignant process
- (4) Accumulations of hemorrhagic fluid, pericardial and pleural
- (5) Suggestive roentgen observations

In many instances, symptoms of cardiac origin are absent. One can readily see that a small fibroma of a valve or a moderate number of nodules in the myocardium would have little effect on the efficiency of cardiac action, but, as previously mentioned, it is astounding how large the tumors may become, how numerous the nodules or how extensive the infiltration of the myocardium before cardiac function is disturbed. This is particularly true of metastatic growths, in such cases usually death occurs as a result of a widespread malignant process. However, even when the growth is primary in the heart, death may occur as a result of distant secondary lesions without cardiac failure. The case of Beck and Thatcher illustrated well how minor the cardiac symptoms may be and yet how severe the involvement of the heart. The patient was a man, aged 27, in whom the symptoms were all abdominal associated with marked cachexia. There were many subcutaneous nodules demonstrated to be spindle cell sarcoma and thought to be metastatic. There was a soft systolic murmur over the precordium, the heart rate was 120 and regular, and the blood pressure, 96 systolic and 56 diastolic. These observations were no different than those that might be found in any terminal cachectic state. Death resulted from general peritonitis. The heart and pericardium weighed 1,100 Gm, 250 cc of blood was

found in the pericardial sac. There was an extensive sarcoma of the left auricle, several centimeters thick, breaking into the cavity of the auricle and almost filling it as two masses, the sarcoma extended over the left ventricle, and involved the outer portion of the myocardium. A purulent general peritonitis was found, due to perforation of the ileum from a huge sarcomatous mass involving the intestines.

In some cases cardiac insufficiency has been part of the terminal picture, subsequent to a clinical course which did not include symptoms of cardiac breakdown. In such cases the heart has appeared to disintegrate in the final stage of visceral dissolution, and there has not been reason to suspect other disease of the heart.

Symptoms of congestive heart failure develop in a certain percentage of cases, and the clinical course may be entirely that of cardiac decompensation. Usually in such instances the clinician is unable to determine the etiologic factor that is responsible for the heart failure, or he may assign a cause for which he has insufficient evidence. Extensive involvement of the myocardium, obstruction of an orifice or embarrassment of cardiac activity by a pericardial effusion may result in congestive heart failure. Not infrequently with pedunculated intracavitary tumors an orifice, frequently the mitral, may be occluded and the signs of stenotic valvular disease be imitated. In such cases, the diagnosis is given as cardiac decompensation due to chronic endocarditis. The careful clinician may be able to detect certain peculiarities in these cases, these peculiarities will be discussed shortly. An interesting observation has been made that the smaller benign neoplasms are often found in cases in which persons have died of cardiac failure, and in which the tumor could not possibly have played a causative rôle.

Sudden death has occurred in some of the cases reported, either in the course of symptoms of cardiac insufficiency or in the absence of any cardiac symptoms. Usually the sudden death has been apparently due to sudden occlusion of either the mitral or the tricuspid orifice by the penetration of an intracavitary pedunculated tumor. Although strands of cancer cells have been noted loose in the coronary vessels (Moore), and neoplastic thrombosis of the cardiac chambers has been noted (Kanthack, Aubertin, Waithin), it is questionable whether any of the sudden deaths recorded have been caused by metastatic emboli occluding the coronary arteries. Anginal attacks have occurred, in the case reported by Ingram they were followed by sudden death, but it was questionable whether the carcinomatous nodules that had formed in the heart had caused obstruction of the coronary arteries. In the case of Fuhman (case 1) in which a spindle cell sarcoma of the aortic valve had obliterated the orifice of the right coronary artery and the left coronary artery had been occluded by a plug of tumor tissue, sudden death occurred without previous symptoms except headache.

In a limited number of cases a clinical course practically identical to that of subacute bacterial endocarditis has been recorded. These are usually cases of carcinomatous metastasis involving the cavity of the heart and throwing off showers of small emboli from time to time into the circulation. Examples of this type of course are the cases of Rist and Rolland, of Widal and Abrami and of Carnot and Lambling. The blood culture, of course, is not positive, but this fact is not of great diagnostic importance in bacterial endocarditis and would therefore not be sufficient to rule out this more common condition.

Thus far there has been nothing of diagnostic value in the clinical types discussed. There are, however, clinical features that in certain cases should make one include tumor of the heart in the differential diagnosis. In every case of heart block, especially when complete, one should consider the possibility of tumor when there is no definite cause ascertainable for the arrhythmia. Two cases of lymphangio-endothelioma of the auriculoventricular node causing heart block have been described. Armstrong and Monckeberg's patient was a boy, aged $5\frac{1}{2}$ years, with intermittent complete heart block. In Lloyd's case the patient was a syphilitic Negro, aged 39, with first degree heart block, who died suddenly while being examined. A relatively large number of secondary tumors have been described in which some portion of the conduction system has been involved. The case of Rosler was diagnosed during life as heart block due to metastatic carcinoma, in the ventricular septum under the aortic valve was a walnut-sized metastatic tumor occupying the entire thickness of the septum. A woman, aged 47, had a carcinoma of the cheek with metastases in the right deltoid muscle, while she was in the hospital, precordial pain, a sense of oppression, dyspnea and a feeling of occasional cardiac standstill developed. The heart was not enlarged, the rate was 26 per minute, there was a loud systolic murmur at the apex. Stokes-Adams' attacks occurred in a case carefully described by Luce. In the case reported by Willius and Amberg, the diagnosis of secondary sarcoma of the heart was made during life because of cardiac failure and great hypertrophy of the heart developing in a child known to have a sarcoma of the femur, the electrocardiogram of "left bundle branch block" was obtained. In some instances it has been a matter of wonder why disturbances in conduction were absent in the presence of extensive involvement of the inter-ventricular septum (case of Martin and Klotz). Arrhythmias other than complete heart block are not infrequent but are of no diagnostic value, although in three cases reported by Fishberg the appearance of auricular fibrillation in two and auricular flutter in one associated with orthopnea led to the diagnosis of metastatic invasion of the heart.

When one considers other signs or symptoms referable to the location of the tumor, one finds that certain suggestive evidence is

occasionally manifested. Anomalies of the symptomatology of cardiac disease are not infrequent in tumors of the heart and should lead to careful consideration of etiology. For instance, if a tumor of the left auricle involves the pulmonary veins there may be great embarrassment of the pulmonary circulation, with dyspnea, cyanosis and cough greatly out of proportion to the degree of edema (case of Justi). In one of Binder's cases in which the right auricle was nearly filled by a primary sarcoma, the edema began in the face and extended next to the thorax and lastly to the legs. Likewise in Ehrenberg's case there were dyspnea, cyanosis and edema of the upper half of the body with enlargement of the veins of the sternum, the tumor filled the right auricle and the venae cavae. Often, because of these signs of obstruction of a certain part of the cardiac apparatus, and when the area of cardiac dulness is greatly increased, the diagnosis of tumor of the mediastinum is made. This is especially true in cases of large sarcomas. The symptomatology of large, pedunculated, intracavitary tumors, which are usually of myxomatous and sometimes of sarcomatous nature, is of particular interest. The tumor frequently penetrates and therefore greatly occludes an intracardiac orifice, usually the mitral, less often the tricuspid, and sometimes the pulmonary and aortic. A number of cases of this type, in which the mitral orifice has been obstructed, have been observed. Mitral stenosis or regurgitation have been simulated. Several features, however, may be present to indicate that the case is not the usual one of rheumatic endocarditis. The history of a rheumatic infection is absent, when congestive failure begins, it is progressive, digitalis usually has no effect, and the physical signs may change with change of position. In this last respect the signs may be those of mitral stenosis when the patient is sitting and of mitral insufficiency when he is recumbent, or the murmur may change remarkably within a short time. Gottel quoted Pavlovsky's case of a primary sarcoma of the right auricle, in which during life the diagnosis of a primary tumor of the left auricle had been made, because the signs were those of stenosis when the patient's body was vertical and those of regurgitation when it was horizontal. Sudden attacks of intense dyspnea or paroxysms of cyanosis may occur with change of position. Signs of right auriculo-ventricular obstruction should arouse suspicion because tricuspid stenosis resulting from inflammation of this orifice is so rare. Likewise, tumor of the heart should be considered when signs of pulmonic stenosis are acquired, since this lesion is almost always congenital. The sessile intracavitary tumors do not often produce these clinical pictures, but occasionally they obstruct an orifice. In sarcomatous intracavitary growths, multiple emboli may be thrown out into either the pulmonary or systemic circulation.

Occasionally, when a person has a recognized malignant neoplasm, the onset of symptoms of cardiac dysfunction, such as arrhythmia or dyspnea or passive congestion, suggests the possibility of metastatic invasion of the heart. Naturally other causes for the cardiac symptoms must be eliminated. In all of the cases thus far diagnosed during life as secondary invasion of the heart, such a situation has existed. The case of Rosler, that of Willius and Amberg, and the three cases reported by Fishberg were diagnosed in this way. The patients of the last named author were all aged between 60 and 70. Two had known primary carcinoma of the bronchi, and auricular fibrillation, orthopnea and finally cyanosis developed. In both, the carcinoma had invaded the posterior wall of the right auricle (in one, also the left) down to the endocardium sufficiently extensively to destroy a large part of the auricular wall and probably the sino-auricular node. In the third case auricular flutter, status anginosus and orthopnea developed in a man with widespread sarcoma of the reticular cells. The walls of the right auricle were extensively invaded down to the endocardium and a nodule 2 cm in diameter surrounded and obstructed considerably the circumflex branch of the left coronary artery.

The accumulation of bloody fluid in the pericardial sac is highly presumptive evidence of a tumor of the heart. This is a not uncommon finding in sarcoma of the heart in which the epicardium is involved or in which the growth begins in the pericardium. Tumor cells may rarely be found in the fluid. Bloody pleural effusions, while not as definitely suggestive of a cardiac neoplasm, should arouse one's suspicion.

Lastly, a localized enlargement of the heart or an irregularity in its outline associated with enlargement should make tumor of the heart one of the main considerations, together with aneurysm of the heart and mediastinal tumor. These irregularly enlarged hearts have usually been diagnosed mediastinal tumor. The fluoroscope or roentgenogram is naturally of paramount importance in detecting localized enlargements and irregularities.

SUMMARY AND CONCLUSIONS

Tumors of the heart and pericardium, both primary and secondary, are rare. Metastatic lesions are usually carcinomatous or sarcomatous, and are seen most commonly in cases of widespread dissemination. The primary growth may occur in any organ. Invasion of the heart apparently occurs most commonly by way of the blood stream, and the right side of the heart is more often or more extensively involved than the left.

Primary tumors of the heart are myxoma, fibroma, sarcoma, rhabdomyoma and less commonly lipoma, endothelioma and a few rare forms.

Valvices occur in the heart. Nodular leukemic infiltrations are occasionally seen. The myxoma is a pedunculated intracavitary tumor and often reaches sufficient size to obstruct an auriculoventricular orifice. The fibroma is a pedunculated valvular tumor and never becomes very large. The sarcoma may be intramural or intracavitary or both and often becomes extensive. Metastases from sarcoma of the heart are relatively not uncommon. The rhabdomyoma is a congenital tumor of embryonic cardiac muscle and is often associated with tuberous sclerosis of the brain and other developmental disturbances. The patients usually die in infancy or early childhood of conditions not referable to the heart. The lipomas are rarely the cause of cardiac dysfunction. Lymphangioendothelioma of the auriculoventricular node may occur and cause auriculoventricular dissociation.

Primary tumors of the pericardium are usually sarcoma or lipoma. Other tumors have rarely been described, including carcinoma or endothelioma of the surface cells of the epicardium.

The symptomatology may be divided into two classes—that which is not suggestive of tumor of the heart and that which is. In the first class are those cases in which there are no symptoms referable to cardiac dysfunction, those in which there is terminal cardiac breakdown, those in which symptoms of simple congestive heart failure dominate the clinical picture, those in which sudden death occurs with or without previous cardiac symptoms and those in which the clinical picture is that of subacute bacterial endocarditis. In the second class the clinical types may be quite diverse but should serve to call to mind the possibility of tumor of the heart. Any case of heart block in which no satisfactory explanation of the arrhythmia is obtainable may be one of tumor breaking through or originating in the main portion of the conduction apparatus. When symptoms referable to disturbance of function of a portion of the heart occur, tumor of that part of the heart is a diagnostic possibility. In the case of pedunculated intracavitary tumor obstructing a cardiac orifice, usually the mitral or tricuspid, certain deviations from the usual symptomatology of endocarditis are often present. The history of rheumatic infection is absent, the course of congestive failure is progressive, there is little or no response to digitalis, and the physical signs may change remarkably with change of posture. In every case in which tricuspid stenosis seems to be present, tumor should be suspected because inflammatory stenosis of that orifice is exceedingly rare. Acquired pulmonic stenosis should be considered the result of neoplastic obstruction. If in a person who is known to harbor a malignant neoplasm cardiac symptoms develop which cannot be otherwise explained, it is reasonable to assume that metastatic invasion of the heart has occurred. Accumulations of hemorrhagic fluid in the pericardium are

suggestive of subepicardial or pericardial neoplasm, and hemorrhagic pleural effusions are not uncommon in malignant disease of the heart or pericardium. A localized enlargement of the heart or an irregularity of outline associated with enlargement as shown in the roentgenogram are suggestive of tumor of the heart as well as aneurysm and mediastinal tumor.

Few cases of tumor of the heart have been diagnosed during life. Gottel gave Pavlovsky credit for the diagnosis during life of a primary tumor of the left auricle, which in reality was in the right auricle. Rosler and Willius and Amberg made the diagnosis of metastatic invasion, and Fishbeig reported three cases of secondary involvement of the heart diagnosed or at least considered a probability while the patients were alive.

Appended are the reports of nine cases of tumor of the heart, five of which are instances of secondary tumor and four of primary tumor.

REPORT OF CASES

CASE 1—*Metastatic carcinoma*

In a Negro, aged 55, a simple deteriorating senile type of psychosis developed in September, 1928. On admission to St. Elizabeth Hospital, it was noted that a tumor the size of two fists, rather soft, mushy and conical, with an ulcerated apex, was located on the left side of the chest posteriorly. This tended to bleed easily, and was considered inoperable. The mass grew rapidly, and the patient gradually declined, dying of bronchopneumonia. The sarcoma on the back had grown to more than 2 Kg. in weight, was sharply outlined, almost encapsulated, and did not seem to be infiltrating the tissues. Microscopically, it showed a rather unusual type of fibroblastoma with extraordinary differentiation. The lungs were not consolidated, but a small metastatic carcinoma was found in the peripheral portion, and some of the hilar lymph nodes were infiltrated. The liver and spleen were not affected. The peritoneum and the kidneys were free. Microscopically, a small carcinomatous nodule was found in the prostate, along with adenomatous hyperplasia. A small primary carcinomatous nodule was found in the pituitary. The anterior surface of the heart showed broad confluent patches of opacity. On the posterior surface of the heart were small nodules extending from the epicardium. The cardiac vessels showed patchy sclerosis. On section the cardiac muscle was firm and fibrous. Microscopic examination showed that the nodules in the heart were of metastatic carcinomatous nature, possibly arising from the primary growth in the prostate. There were clumps of cells rather close together, but separated by one or a few cardiac muscle fibers. These clumps of cells were enclosed in a delicate endothelial sheath, apparently that of a greatly dilated capillary. Mitotic figures were moderately numerous.

CASE 2—*Metastatic carcinoma*

A white man, aged 66, was sent to St. Elizabeth's Hospital on account of a suicidal attempt. He was somewhat confused and feeble, and was the subject of paralysis agitans. A roentgenogram of the chest showed a circular opacity in the upper lobe of the right lung which could not be demonstrated by physical examination. After four months with a septic temperature and great

emaciation, the patient died in October, 1930. Necropsy disclosed primary carcinoma of the upper lobe of the right lung with marked degeneration and hemorrhagic infarction. There were secondary nodules in the pleura, the mediastinal lymph nodes and the liver. The heart, besides being rather fibrotic, contained a small shotlike, pearly gray nodule embedded in the anterior wall of the left ventricle. A similar nodule was found in the anterior papillary muscle of the left ventricle and a third superficially in one of the columnae carnae at the base of the right ventricle. Microscopically, the tumor in the lung consisted of polygonal and spindle-shaped cells of unequal size with many gigantic nuclei and numerous mitotic figures. The nodules in the heart consisted of circumscribed masses of similar cells growing between the muscle fibers. In the brain there was secondary implantation in the ependyma in many locations.

CASE 3—*Metastatic carcinoma*

A man, aged 53, had been admitted to St. Elizabeth's Hospital at the age of 35, having developed mental symptoms while in the army. In 1906, his left side became paralyzed. In 1914, he began to pick constantly at an abrasion on the left side of the nose. The lesion gradually increased in size. On March 13, 1924, he had a sudden attack of abdominal pain, and died about seven hours later. Necropsy revealed an extensive basal cell carcinoma involving the left orbit and side of the face. There was no involvement of the brain. The peritoneal cavity contained a liter of cloudy greenish fluid, and disclosed active peritonitis due to the perforation of the cardiac end of the stomach by a large carcinomatous lesion. There was extensive carcinomatous metastasis to the peritoneum, but none to the liver. Some of the esophageal lymph nodes were invaded by carcinoma. The lungs were not involved. The heart weighed 470 Gm., was enlarged to the left, and surrounded by 230 cc. of clear pericardial fluid. The organ was greatly distorted, the entire auricular musculature being infiltrated by malignant growth. The walls of the left ventricle were also greatly thickened, and in areas surrounding the coronaries there were dense thickened patches of infiltration. A malignant polyp with a small attachment was found hanging free in the right auricle. There were undoubtedly two distinct lesions, the basal cell carcinoma of the face and the primary adenocarcinoma of the stomach. No slides are available for a review of the case to indicate which of these lesions gave rise to the carcinomatous metastasis in the heart.

CASE 4—*Hypernephroma of the right auricle*

An elderly Negro of unknown age entered the Gallinger Municipal Hospital in a greatly emaciated, anemic and weakened condition, and died five days later on April 29, 1928. Necropsy revealed the following conditions. There was a large mass in the right renal region, adherent to the liver, the ascending colon and the duodenum, and apparently originating from the kidney. Dissection showed that the mass was a large hypernephroma (clear celled carcinoma) practically replacing the kidney. The new growth had migrated out through the renal vein, passed up through the vena cava, and terminated in the right auricle, which it practically filled as a yellowish, friable mass (fig. 1). The heart was small and the pericardium contained about 100 cc. of clear fluid. The epicardial fat showed serous atrophy. The coronary arteries were markedly sclerotic. Except for the changes due to coronary sclerosis, the myocardium was normal. The orifices of the heart appeared normal. No other metastases were found. The lungs were edematous.

This case is similar to one observed by me at the Mayo Clinic in 1928, in which the hypernephromatous tissue after filling the right auricle passed upward

through the superior vena cava to the veins of the right side of the neck. There were also large metastatic nodules in the lungs in that case. Clinically, there was no evidence of congestive heart failure, as one might expect.

CASE 5—*Metastatic melanosarcoma*

A white man, aged 64, had been confined to St Elizabeth's Hospital for a mild psychosis since 1922. In 1929, the left eye was removed because of severe pain, and examination revealed sarcoma of the choroid penetrating through the sclera and appearing outside the bulb. Recurrence produced a fungating tumor in the orbit. In spite of removal and cauterization, it grew to be the size of a grapefruit. Roentgen examination showed the entire left orbital bony structure replaced by



Fig 1 (case 4) —Hypernephromatous tissue completely filling the right auricle through the inferior vena cava

tumor and metastases in the lungs. Death occurred on Nov 24, 1930. Necropsy showed extension of the original growth into the left malar bone, left antrum, lateral portion of left nasal fossa, and through the orbital plate into the cranial cavity. A metastatic mass about 4 cm in diameter was present in the left temporal lobe. In the left lung was a massive black metastatic lesion, 9 by 8 by 6 cm, and a small one near the hilus of the right lung. A large mass was found medial to the left kidney. Nodules as large as 6 cm in diameter were present in the omentum adherent to the peritoneal coat of the intestine, particularly in the region of the cecum, and there was one small nodule in the submucosa of the colon. Two nodules were embedded in the tail of the pancreas. The heart was of normal size, the epicardium was rather fatty, and the myocardium was soft, fine in texture and translucent. In the posterior part of the interauricular septum on the right side, fairly close to the auricular appendage, were two small shotlike

nodules resembling embedded lead shot, occupying the muscular tissue and showing through into the cavity. Microscopic examination showed that the primary and larger secondary lesions consisted of groups of cells containing a variable amount of pigment, tending to necrosis in the center and to widespread extension externally. The nodules were rather richly supplied by thin-walled blood vessels. The small nodules in the heart consisted of a mass of similar cells infiltrating the auricular musculature (fig 2). The nuclei of the cells were large and hyperchromatic. The tumor was a melanosaarcoma. A microscopic metastatic nodule

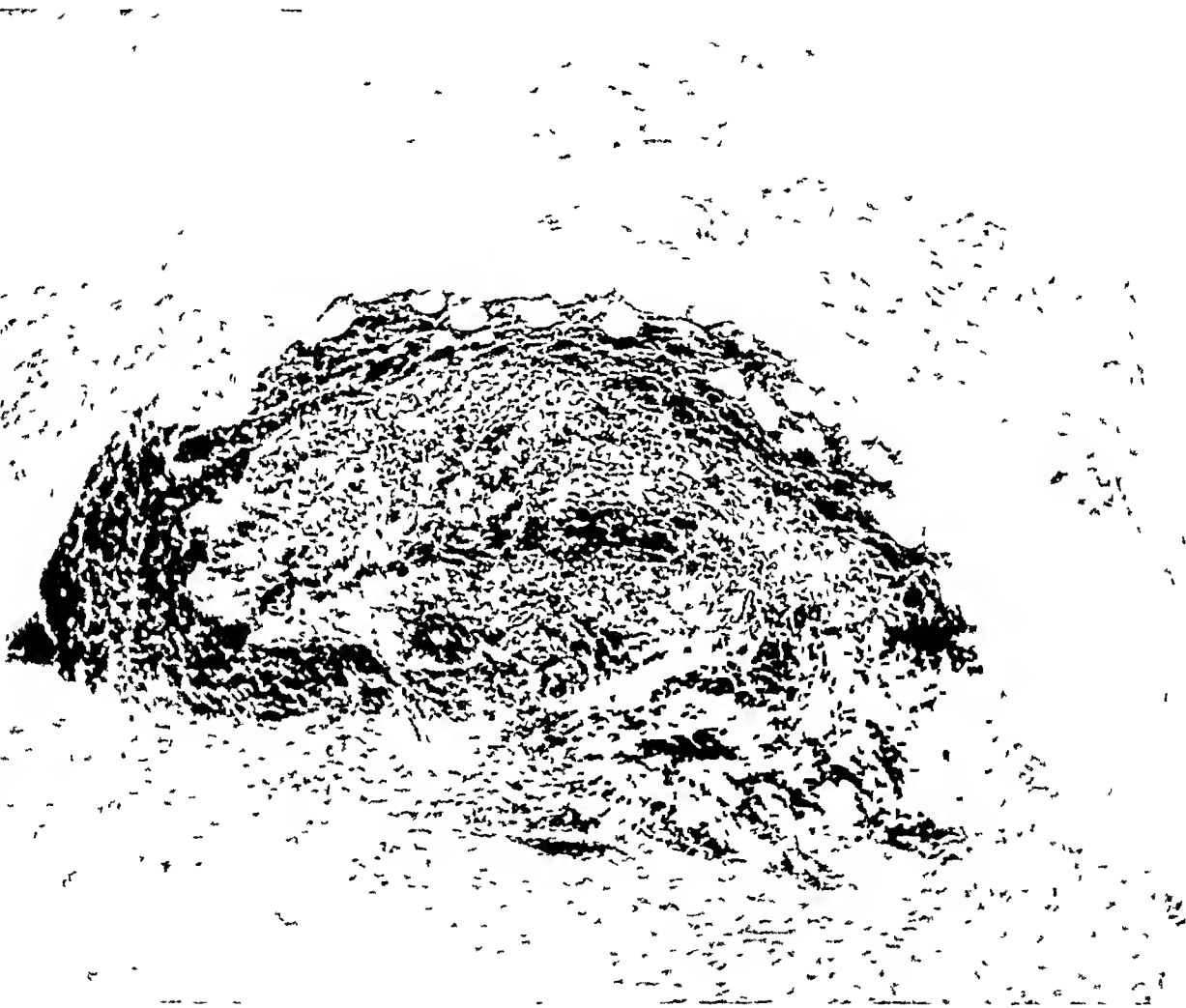


Fig 2 (case 5)—Photomicrograph of metastatic melanosaarcoma in the wall of the right auricle, reduced from a magnification $\times 85$

was found in the suprarenal. In addition to the primary growth of the eye with its multiple metastases, there were a papillary cystadenoma of the renal cortex of doubtful malignancy and a small primary growth probably of adenocarcinomatous type in the hypophysis.

CASE 6—*Myioma of the left auricle*²

A woman, aged 23, came to the clinic on June 16, 1927, complaining of shortness of breath, palpitation and weakness for a period of two years. The onset

² This case has been previously reported (Barnes and Yater. *M. Clin. North America* **12** 1603, 1929)

of symptoms had not been acute or definite, they had become distinctly worse in the last six months with some swelling of the ankles and feet at the end of the day. Nausea, vomiting and gaseous distention in the epigastrium constituted the chief complaint on admission. The previous history was not significant, and rheumatic infection was not known to have occurred.

Examination of the heart showed a presystolic murmur and thrill at the apex and a systolic apical murmur transmitted to the axilla. The second pulmonic sound was markedly accentuated. There was moderate cyanosis of the lips and nails. The laboratory data were not significant, except that a teleoroentgenogram showed evidence of definite cardiac enlargement. The electrocardiogram showed a rate of 80, a notched Q R S wave in derivation III and left ventricular preponderance.



Fig 3 (case 6) —Pedunculated myxoma of left auricle, bisected, showing hemorrhages in the substance of the tumor

The patient's response to the administration of digitalis and to every effort at treatment was not satisfactory, and her course was progressively downward. She died from cardiac failure twenty-nine days after admission.

The usual conditions of chronic passive congestion of the liver and spleen, ascites and hydrothorax, and pulmonary infarcts were found. The heart weighed 374 Gm. In the left auricle, attached by a broad base to the interauricular septum in the region of the fossa ovalis, was an elongated, irregularly round, gelatinous looking tumor which measured 6 by 4.5 by 3.5 cm. It practically filled the auricle and its lower fourth almost occluded the mitral orifice. On the surface of the tumor were a few small areas of hemorrhage, when the mass was bisected, the cut surface resembled colloid material and was hemorrhagic (fig 3). The

ventricles were both markedly dilated, particularly the right, and the walls of the latter chamber were considerably hypertrophied. The valves appeared normal except for small terminal vegetations on the tricuspid. The coronary arteries were smooth. This was microscopically a myxoma. Stained with hematoxylin-eosin, the matrix was a pale, pinkish, granular or fibrinous substance. In it were numerous cords of endothelial-like cells, often appearing like a syncytium. The

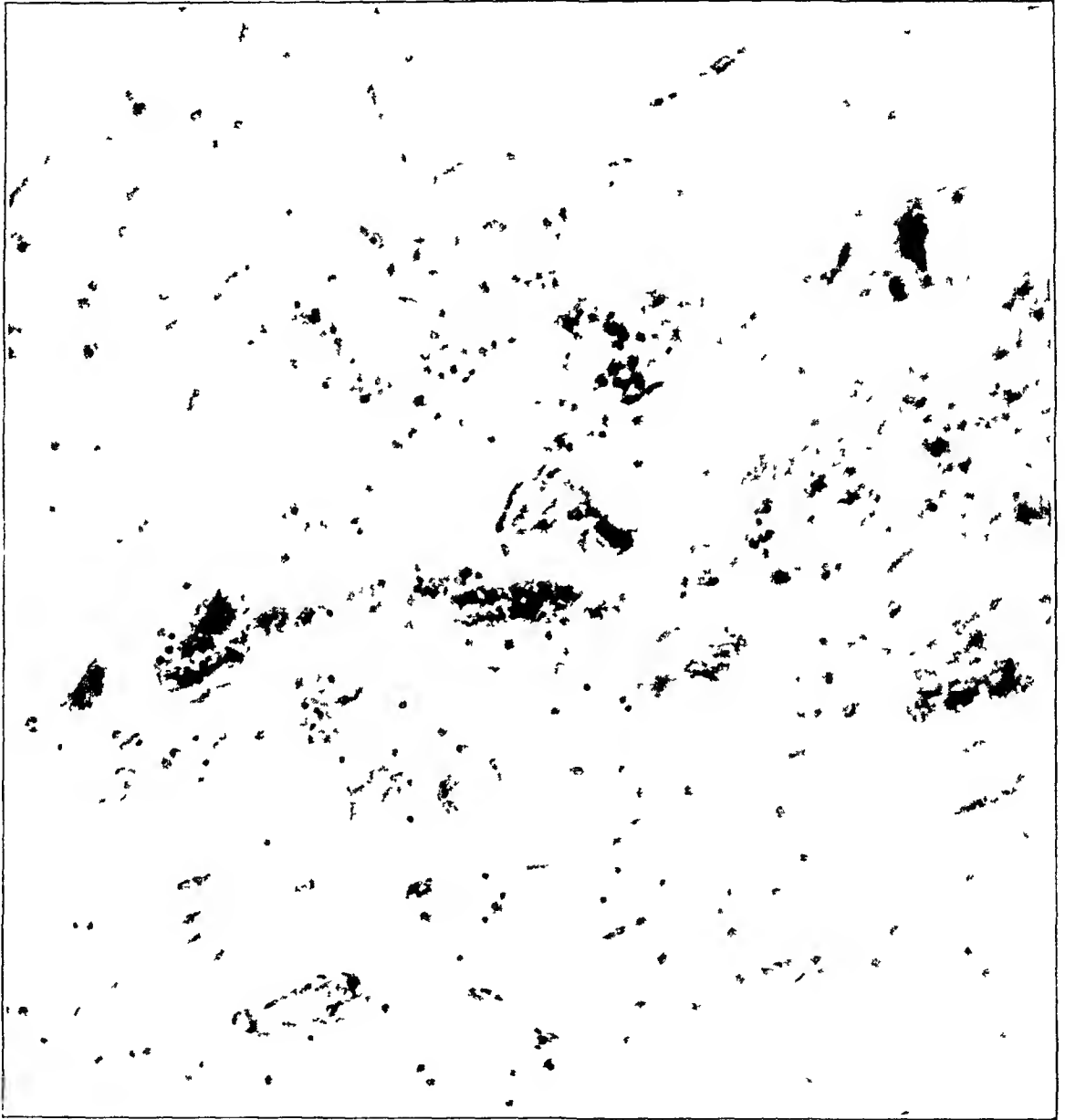


Fig 4 (case 6) —Photomicrograph of myxoma, showing small hemorrhages and cords of endothelial-like cells in a mucoid matrix, $\times 225$

nuclei were light, oval, vacuolated and rather large. These groups of cells were in general placed with their long axis in the same direction. They tapered at the ends, the nuclei were numerous and close together, and the cytoplasm was rather pale. Delicate blood vessels were present in the tumor, but were not especially numerous. One contained a fibrinoid thrombus. Groups of erythrocytes were scattered through the sections, and were more numerous toward the center of the

tumor (fig 4) Hemosiderin was present in the cytoplasm of some of the cellular syncytia and in what appeared to be plasma cells scattered through the sections Lymphocytes were seen here and there, and less numerous polymorphonuclear leukocytes occurred, clumped in small groups widely separated

Both grossly and microscopically, this case closely resembled another case studied by me in 1928 at the Mayo Clinic In that case, however, the patient a woman, aged 34, died of septicemia following a self-induced abortion She had increasing but not especially severe dyspnea on exertion for two years and a systolic apical murmur

CASE 7—*Hyaline fibroma of the aortic valve*

A Negro, aged 70, entered the Georgetown University Hospital in a greatly emaciated condition Two months previously, speech had become impaired and

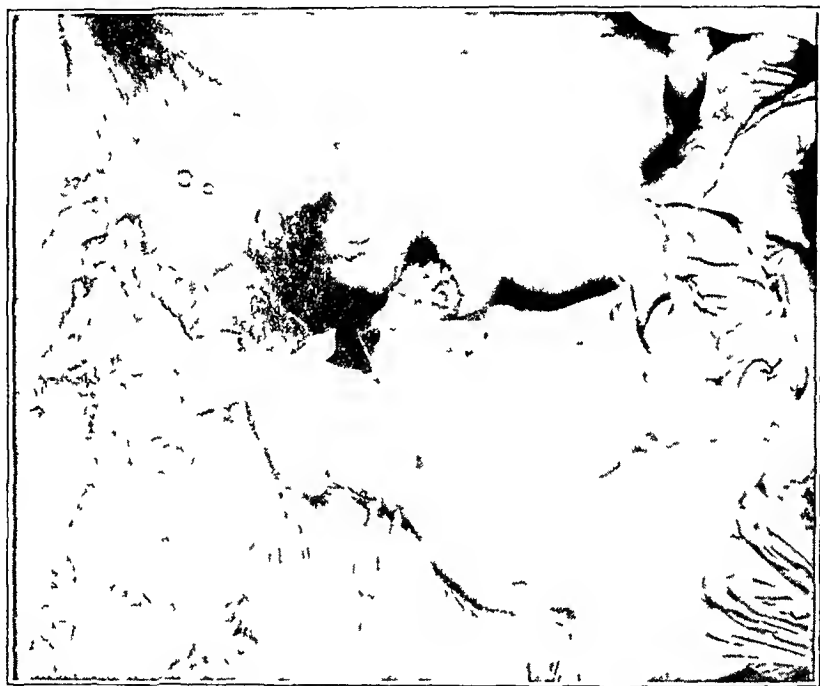


Fig 5 (case 7) —Papilloma (hyaline fibroma) of the aortic valve

ability to walk was lost Examination revealed a rapid, feeble pulse, generalized moist râles in both lungs, inability to articulate or swallow and right hemiplegia Death occurred three days after admission, May 6, 1929 Necropsy revealed nothing of unusual interest except in the heart On the edge of the noncoronary cusp of a somewhat sclerotic aortic valve, projecting up into the aorta when the valve was closed, was a rounded, extremely villose, grayish-pink tumor, about 0.8 cm in diameter, attached to the valve by a short pedicle (fig 5) Microscopically, this papilloma was seen to spring from the subintimal connective tissue by several small roots The valve in this region was microscopically otherwise normal The tumor was completely invested by a single layer of endothelial cells continuous with the intima of the valve It was completely avascular (fig 6) The ground substance was homogeneous, pale and slightly eosinophilic (hematoxylin-eosin stain) Some of the villi contained denser centers of circular or oval shape, which showed dense accumulations of broken elastic fibers arranged in layers (Weigert's elastic stain) In the ground substance of some of the villi

were a few, somewhat round cells with an ovoid, rather dark often eccentric nucleus and a fair amount of cytoplasm. The matrix of the tumor stained light purple with van Gieson's stain. Other special stains did not show anything of unusual interest. This tumor might be designated a hyaline fibroma.

CASE 8—*Fibromyoma of the aortic valve*

A white man, aged 65, entered the Georgetown University Hospital on Nov. 15, 1930, and died on November 23, of empyema of the left pleural cavity. Clinically, the case was interesting because the empyema was due to the colon bacillus,

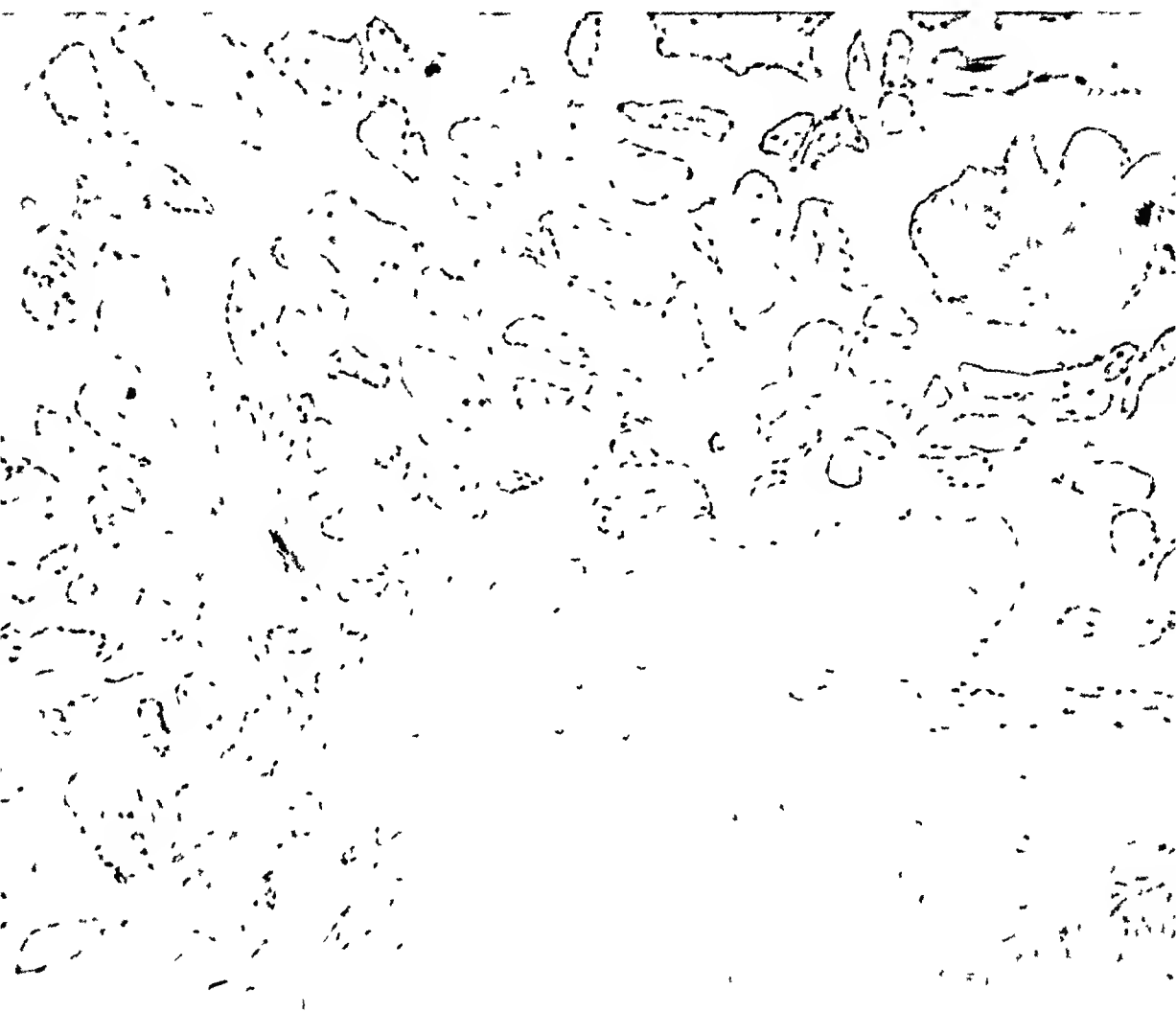


Fig. 6 (case 7)—Photomicrograph of papilloma of the aortic valve through the pedicle, reduced from a magnification $\times 112$

otherwise there was nothing especially remarkable except that the patient gave a history suggestive of duodenal ulcer. Necropsy revealed the empyema and a large duodenal ulcer. The heart was normal except for a papilloma attached by a short, delicate pedicle on the aortic side of the right coronary cusp of the aortic valve near the free edge and 0.5 cm. from the posterior commissure of the cusp. It was pink, villose, soft, rounded, freely movable and a little under 0.5 cm. in diameter. Delicate Lambl's excrescences were present also on the nodules of Arantius of all three cusps of the aortic valve. There was no evidence of inflammatory change. Microscopically, the tumor was seen to resemble closely that in

case 10, which it resembled grossly also. It was a papillary fibromyxoma and was completely avascular. The numerous small villi were covered by a single layer of endothelial cells. The matrix streamed forth from the subendothelial connective tissue of the valve through a short pedicle. In most of the villi the matrix was a delicate myxomatous tissue with scattered star cells. In the center of many of the villi the ground substance was more dense, homogeneous, fibrillar or granular and eosinophilic. When stained for elastic tissue, delicate fibrils of elastin and small granules appearing to be products of disintegrated elastic fibrils were seen in these cores.

CASE 9—*Congenital rhabdomyoma*

A colored girl, aged 5, had had convulsive attacks two years before death, but the attacks had not recurred until two days before her final admission to Ancon Hospital. On admission, she was unconscious, and showed twitching of the muscles, especially of the left side of the body. Flaccid paralysis of the left arm with spastic paralysis of the right arm and difficulty in swallowing developed a few days after admission. The muscular twitchings continued, but the child could be partially roused from her stupor. The spinal fluid was clear with five cells, the Wassermann reaction was negative and pressure was diminished. The patient died twenty-two days after admission, on Sept 13, 1927. Necropsy revealed nothing of note except in the brain, kidneys and heart. The convolutional pattern of the cerebrum was normal but there was considerable variation in the depth and width of the individual gyri, many of which showed focal flattening and widening. The distorted areas were extremely firm on palpation, and on section the firm areas presented a smooth white surface which showed no trace of the cortical gray matter. These areas were irregular in shape and were on the average from 1 to 2 cm in longest diameter. They were scattered throughout the cerebral hemispheres and basal nuclei and there were small nodules of similar tissue in the brain stem, medulla and cord, but not in the cerebellum. The tissue of the brain, except in these areas, was slightly congested, but appeared otherwise normal. Microscopic examination of the firm areas showed diffuse gliosis with reduction or absence of nerve cells. The glial tissue was rich in fibrils and the glial nuclei were not excessive in number (tuberous sclerosis). The kidneys appeared normal except for diffuse involvement with yellowish-white, vascular nodules resembling grossly small conglomerate tubercles. Microscopic section showed that these nodules were interesting examples of mixed tumor of the Wilm's type. There were also small cystadenomas in the kidneys. The heart weighed 85 Gm. The muscle was pale brownish red and fairly firm. There was a yellowish-white nodule in the interventricular septum which measured 1 cm in diameter and projected approximately 0.5 cm subendocardially into the left ventricle. There was a smaller, flat, subendocardial nodule in the wall of the right ventricle. On section, the cut surface of the nodules was yellowish white, homogeneous and translucent. They were sharply outlined, but not encapsulated. The valves and chambers of the heart did not show anything else worthy of note. Microscopically, a typical rhabdomyoma was seen in the heart. The subendocardial nodules were well circumscribed, and except in a few small areas were separated from the myocardium by a layer of connective tissue. The nodule in the interventricular septum was separated into two main portions by a trabecular connective tissue, one portion projected into the ventricular cavity subendothelially. Under low magnification, the tumor looked like a strongly reticulated tissue from which most of the sarcoplasm had been dissolved, leaving only the framework of the connective tissue and the nuclei. Van Gieson's connective tissue stain, however,

revealed that there were practically no fibers of connective tissue present. The supposed reticulum constituted the thin sarcoplasmic shells of large, relatively empty cells in which were large, fairly round nuclei lying in a central island of sarcoplasm attached to the shell by a fine supporting network of sarcoplasm. The nucleus was densely granular, and contained a large nucleolus. Some of the cells contained two nuclei in close proximity. The outlines of the cells indicated that the cells varied somewhat in size and shape, but were irregularly round and more or less of the same size. Between these large cells, small, ovoid, dark nuclei were

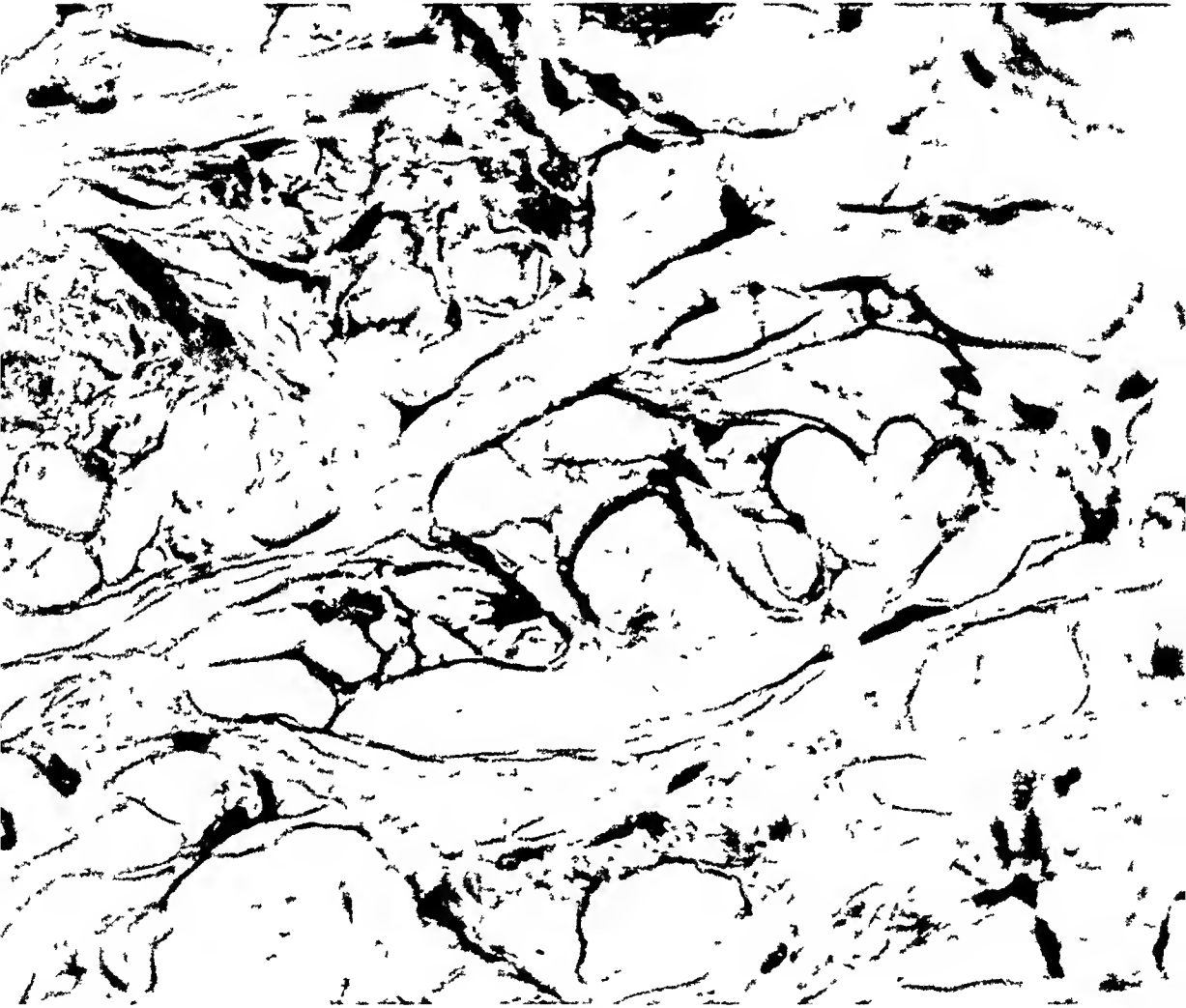


Fig 7 (case 9) —Photomicrograph of a congenital rhabdomyoma of the heart. In the upper left-hand corner is seen an adult cardiac muscle fiber in the midst of rhabdomyoma cells, reduced from a magnification $\times 765$.

intermittently embedded in a little sarcoplasm. Also, occasionally between the large, protoplasmically poor cells, bodies were seen that resembled the nuclei of normal adult myocardial fibers. Where such nuclei were present there might be a denser accumulation of sarcoplasm with parallelly running fibrils, so that a cardiac muscle fiber was suggested (fig 7). Cross-striations were faintly visible in some of these areas. These denser accumulations of sarcoplasm appeared to have more or less the same general direction of their longitudinal axes. At one side of the nodule in the septum, part of the left bundle branch lay exceedingly close to the

edge of the tumor nodule and was barely separated from it by the finest connective tissue fibers. This gave an excellent opportunity to study the two types of tissue, the Purkinje fibers and the rhabdomyoma cells. While there was a superficial resemblance, more careful study showed the two tissues to be quite different. Running through the tumor nodule a few scattered delicate fibrous trabeculae were seen supporting the tissue and the small blood vessels. At the edge of the nodule where the myocardium was in direct contact, a definite transition between the two tissues was not apparent.

NOTE—Since this article was written I have observed two further cases of tumor of the heart.

The first patient was a psychotic woman, aged 69, who was found at necropsy to have a carcinoma of the gallbladder with metastases to the lungs, liver, ovaries, suprarenal glands and heart (St. Elizabeth's Hospital, autopsy no 5631). On microscopic section, two small nodules made up of rather large polygonal cells were found in the heart, they resembled those of the other metastases. One nodule was located in the subepicardial fat, while the other was in the myocardium. Both were infiltrating.

The second patient was a man, aged 51, who was thought to have a primary pulmonary neoplasm with metastases to the liver. At necropsy (Georgetown University Hospital, autopsy no 34-Y-31), a large bronchiogenic carcinoma of the left lung was found which had extended into and replaced the wall of the left auricle down to the endocardium. The tumor of the lung had so surrounded and compressed the pulmonary artery that its lumen appeared like a slit. During life, significant cardiac dysfunction had not been noted. A detailed report of this case will be given elsewhere.

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FUNCTIONAL ASPECTS OF REGENERATED HEPATIC TISSUE¹

T L ALTHAUSEN, M D
SAN FRANCISCO

It is common knowledge that the liver surpasses most, if not all, glandular organs in its power to replace substance lost through disease. The anatomic processes involved in reconstruction of hepatic parenchyma after spontaneous or experimental injury to the liver have been well described by many investigators¹. However, little is known concerning the functional capacity of regenerated hepatic tissue.

A new approach to this important subject was opened by recent progress in tests of renal function, two of which were instrumental in the present contribution to the knowledge of pathologic physiology. The first of these, the rose bengal dye excretion test,² is based on the selective elimination, via bile channels, of this dye when given intravenously. Retention of rose bengal in the blood above 60 per cent at the end of eight minutes and over 30 per cent after sixteen minutes is indicative of decreased permeability of the hepatic cells or of obstruction to the free flow of bile. The second, a modification of the dextrose tolerance test,³ in which insulin and a large amount of water are given to the patient in addition to dextrose, depends on the carbohydrate metabolism-regulating function of the liver. A blood sugar level below 70 mg per hundred cubic centimeters at the conclusion of this test indicates incompetence of the carbohydrate-regulating mechanism of this organ.

These tests, in my experience, covering over sixty cases, have given very similar estimates of the functional state of the liver in health and in various diseases of the liver. However, in five patients with obvious

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From the Department of Medicine, University of California Medical School, San Francisco

1 For a good bibliography see Schultz, E W, Hall, E M, and Baker, H V. Repair of the Liver Following the Injection of Chloroform into the Portal System, *J M Research* **44** 207, 1923-1924

2 Epstein, N N, Delprat, J D, and Kerr, W J. The Rose Bengal Test for Liver Function, *J A M A* **88** 1619 (May 21) 1927

3 Althausen, T L, Gunther, Lewis, Lagen, J B, and Kerr, W J. A Modification of the Glucose Tolerance Test as an Index of Metabolic Activity of the Liver, *Arch Int Med* **46** 482 (Sept) 1930

hepatic disease and marked retention of rose bengal dye, the carbohydrate metabolism-regulating mechanism of the liver was found to be within normal limits, as indicated by the modified dextrose tolerance test. In three of these cases, the histories of which are briefly summarized, the liver was examined pathologically, making it possible to bring them together under one pathologic entity. This entity, namely, toxic cirrhosis of the liver, can now also be recognized clinically by the contrast between evidence of hepatic damage with marked retention of dye and preservation of normal carbohydrate metabolism regulation.

REPORT OF CASES

CASE 1—A Swedish stevedore, formerly a sailor, aged 53, was admitted to the University of California Hospital on Dec 18, 1928, with a complaint of swelling of the legs and abdomen which came on after exposure during a rainstorm five days before entry. This swelling was accompanied by cramplike abdominal pains, dyspnea and palpitation. At the same time he noticed a diminished output of urine, nocturia and distention after meals. He admitted that he used alcohol moderately.

On examination, there was vitiligo on his arms. The cervical lymph nodes were palpable. The right pupil was small and fixed, the left pupil reacted slowly to light and accommodation. There were signs of fluid at the bases of both lungs. The abdomen was distended with fluid, no organs could be felt, even after paracentesis. The patellar and achilles reflexes were absent. Slight pressure on the prostate produced mucopurulent fluid at the urinary meatus. The urine and purulent prostatic fluid were loaded with pus and contained numerous intracellular and extracellular gonococci. An examination of the blood showed a moderate leukopenia with a normal differential count. The Wassermann test of the blood was negative, but the Kahn test was reported 2 plus. The nonprotein nitrogen of the blood was 44.8 mg per hundred cubic centimeters. Fluid having the characteristics of transudate, with a specific gravity of 1.010 and a negative Wassermann reaction, was removed from the abdomen and chest in amounts of 4,000 and 1,400 cc, respectively. A lumbar puncture gave negative results, including the Wassermann reaction. The rose bengal test for hepatic function showed a retention of 95 per cent of the dye at the end of eight minutes, and 83 per cent at the end of sixteen minutes. A modified dextrose tolerance test gave a normal curve with a blood sugar of 83 mg per hundred cubic centimeters at the end of three hours.

Two weeks after the first paracentesis, the abdomen was again distended with fluid. At this time the patient vomited about 250 cc of dark red blood, and a few minutes later also passed blood by rectum. Three days later, he failed to urinate for twenty-four hours. Since multiple strictures of the urethra made catheterization impossible, suprapubic cystotomy was performed, but only 60 cc of urine was found in the bladder. Five hours after the operation, the patient died with evidence of another esophageal hemorrhage. During his stay in the hospital he was afebrile.

The main clinical diagnosis was portal cirrhosis of the liver. At autopsy, performed by Dr J F Rinehart, the liver was found to weigh 1,090 Gm. Its surface was strikingly nodular and granular, having a greenish-yellow appearance. Microscopically (fig 1), it showed a marked fibrosis of irregular distribution and adenomatous areas of hepatic cells. The hyaline droplets described in alcoholic cirrhosis by Mallory were not seen. The kidneys were essentially normal.

The main pathologic diagnosis was toxic cirrhosis of the liver.

CASE 2—An Irish crane operator, aged 45, entered the University of California Hospital on June 8, 1929. He had been well up to three weeks before admission when general malaise and anorexia developed. A few days later the patient noticed a gradually increasing yellow discoloration of his skin, accompanied at times by sensations of fever. At the same time his stools became light, and the urine assumed a very dark color. Five days prior to entry, swelling of the ankles and abdomen appeared.

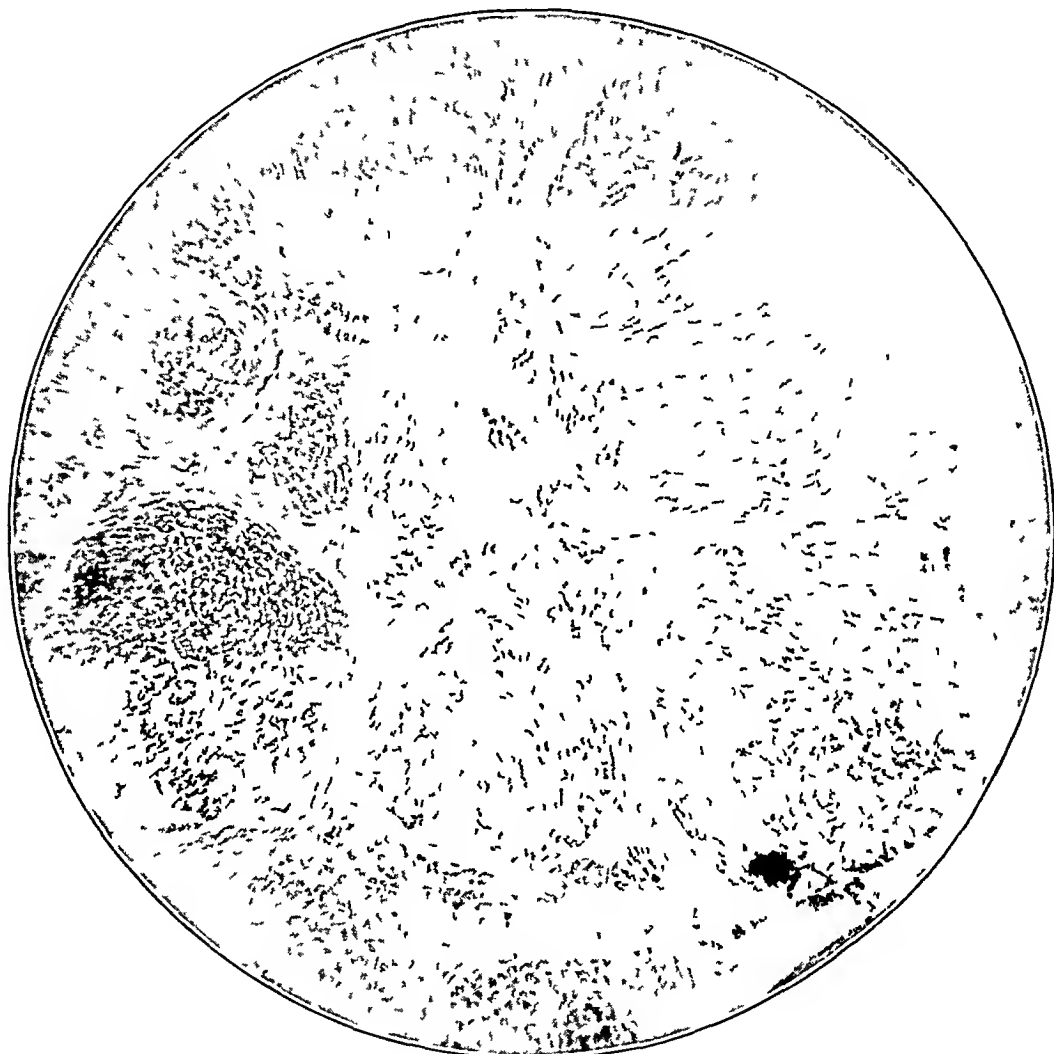


Fig 1 (case 1)—Section of the liver showing marked fibrosis of irregular distribution and adenomatoid areas of hepatic cells, $\times 22$

On physical examination, the patient presented a picture of deep icterus. He had bilateral ptosis of the upper eyelids, more marked on the right. The diaphragm was high, and there were signs of congestion at the base of the right lung. The abdomen was moderately distended, and no organs were felt. There was moderate edema of the lower extremities. The blood showed a leukocytosis of 11,400 with 76 per cent of polymorphonuclear neutrophils. The Wassermann and Kahn tests of the blood were negative. The icterus index was 190. In the urine were found much bilirubin and some urobilin. The stools were light brown. Three days after entry, the patient developed signs of fluid in the abdomen, which was tapped, and

2,200 cc of fluid was obtained. The ascitic fluid was a typical transudate with a specific gravity of 1.008 and a negative Wassermann reaction. A modified dextrose tolerance test showed a normal blood sugar curve with the reading of 122 mg per hundred cubic centimeters at the end of three hours. The rose bengal test for hepatic function was not done in view of deep jaundice. In the hospital the patient grew rapidly worse and, passing through a delirious stage, died on the sixth day in coma. There was a terminal rise of rectal temperature to 38.5 C (101.3 F).

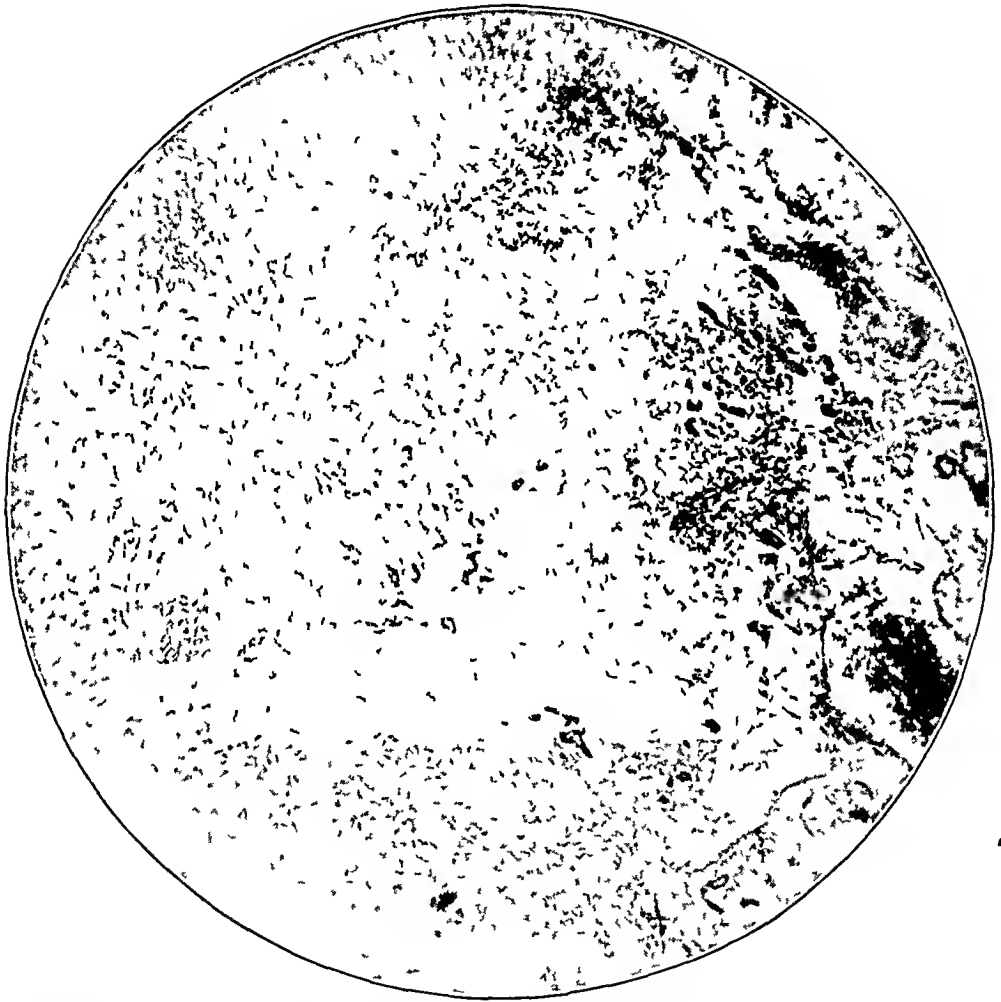


Fig 3 (case 2) —Section of the liver taken from the red marginal zone and showing complete parenchymatous destruction with remaining bile ducts, $\times 48$

The main clinical diagnosis was cirrhosis of the liver (nature undetermined), with cholemia.

At postmortem examination, performed by Dr J. F. Rinehart, the liver was found to be very small, weighing only 840 Gm. Scattered over the surface were small, grayish, elevated nodules (fig 2). On section, the right lobe of the liver showed a narrow marginal zone of red tissue containing minute gray areas. The central portion of the liver was composed of greenish regenerated tissue having a nodular arrangement. Most of the left lobe consisted of dense red tissue, but it, too, contained nodules of regenerated parenchyma.

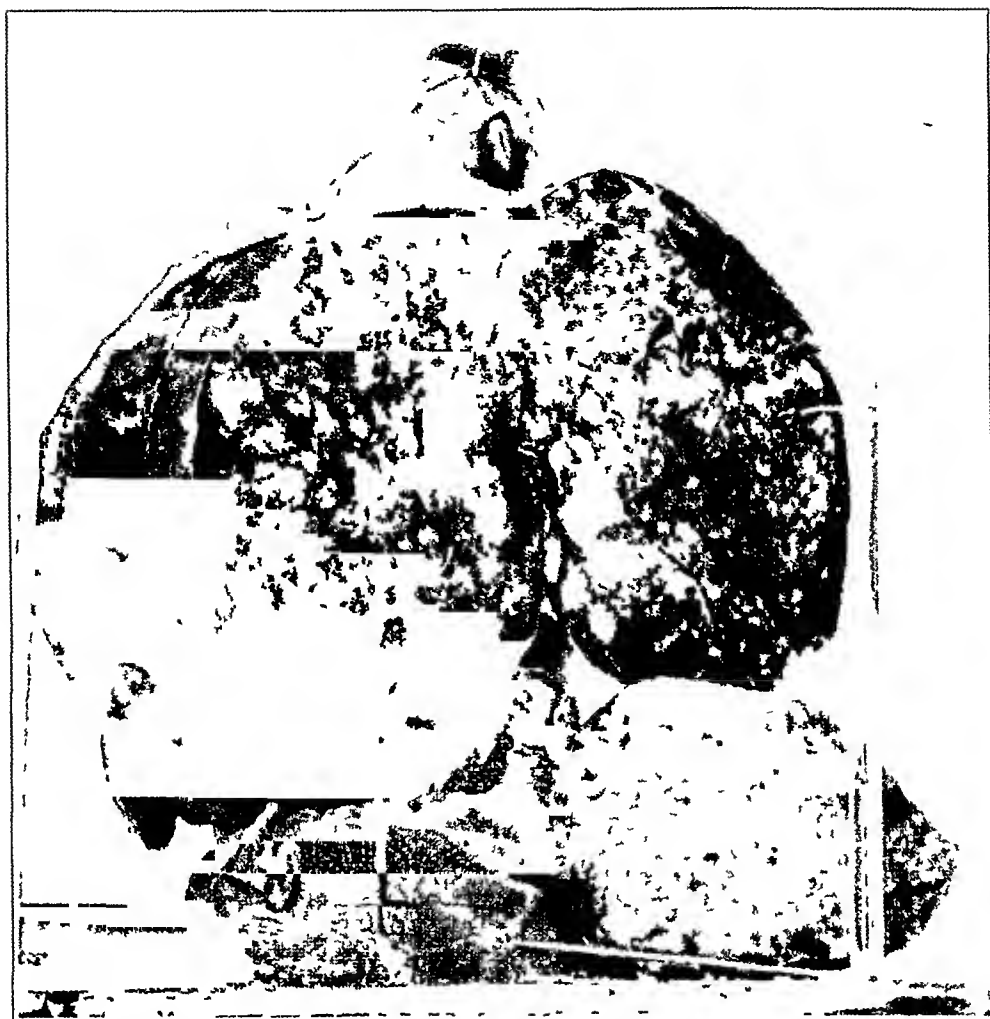


Fig 2 (case 2) —The red marginal zone of the liver shows complete parenchymatous destruction. The central bile-stained portion of the liver represents regenerated hepatic tissue without lobular arrangement.

Under the microscope, the red marginal zone (fig 3) showed complete parenchymatous destruction, but the framework with its portal spaces and central veins remained. Tissue from the central portion of the liver (fig 4) showed hyperplastic nodules of regenerated parenchyma in which lobular arrangement was entirely lost. These nodes of varying size were separated by bands of fibrous tissue. Biliary stasis was distinctly shown in the canaliculi near the margin of the nodules.

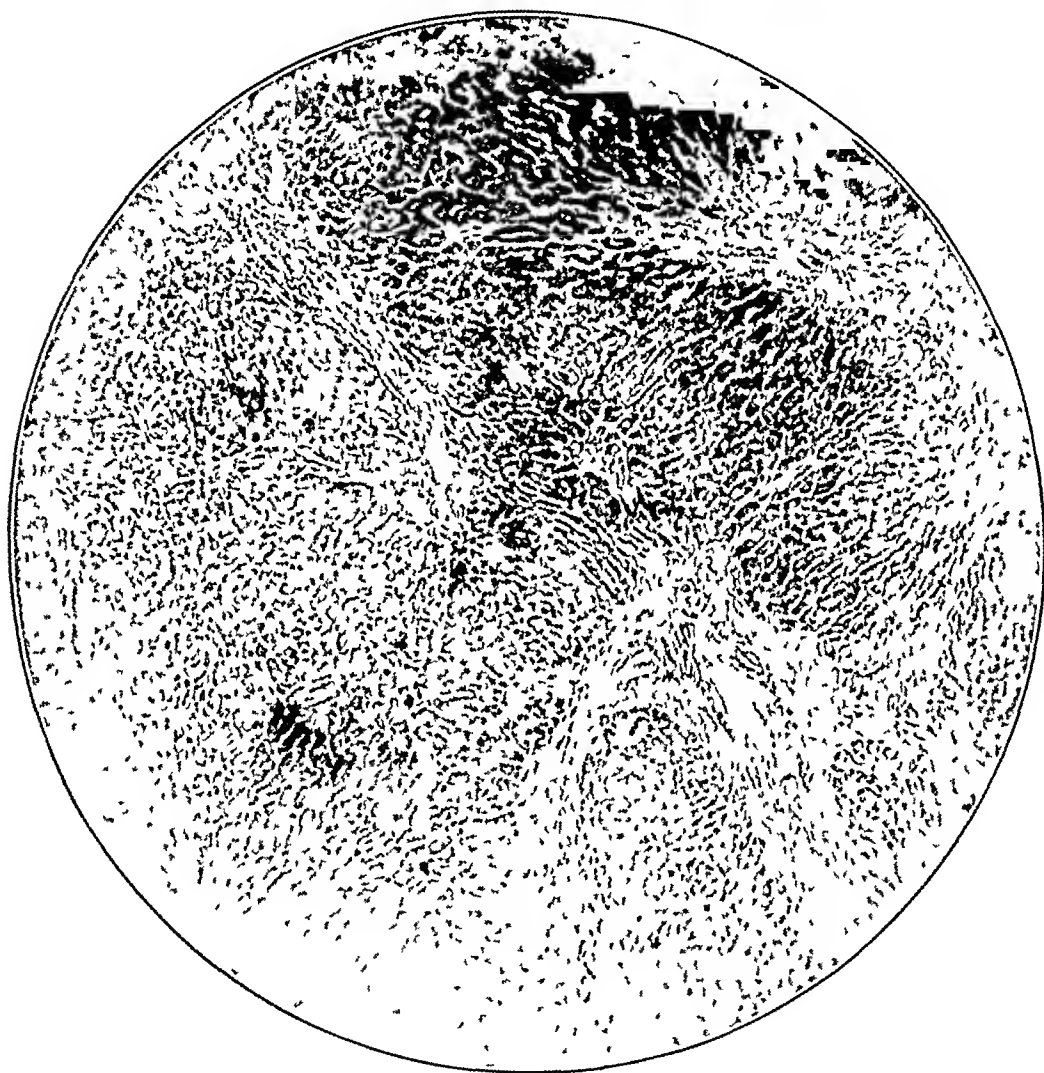


Fig 4 (case 2) —Section of the liver taken from the central portion of the liver and showing regenerated parenchyma without lobular arrangement, $\times 48$

The principal pathologic diagnosis was subacute atrophy of the liver with regenerative hyperplasia and early toxic cirrhosis.

CASE 3—A chorus girl of Norwegian extraction, aged 17, was admitted to the University of California Hospital on Jan 15, 1929, with complaints of jaundice and amenorrhea. Late menstruation and sterility were characteristics of the female members of her father's family. During the past three years, the patient had four or five attacks of jaundice with chills, fever, marked abdominal distention and nausea. The two last attacks were also associated with sharp pains in the right upper quadrant. At the time of entry, she had had generalized abdominal pain

and tenderness for one month and distention for two months. During the past year, the patient had epistaxis two or three times weekly. In her occupation she used as a whitening substance, a toilet preparation, "Shady Glen," all over her body several times a day, instead of once as did the other chorus girls, because this compound underwent greenish-blue discoloration on her skin. On physical examination, she showed moderate icterus and some girdle obesity. The edge of the liver was tender, and the spleen extended 3 cm below the costal margin. The breasts and genitalia were infantile. The blood showed moderate secondary anemia, with a reticulated cell count of 15 per cent. The Wassermann and Kahn tests of the blood were negative. Repeated fragility tests showed normal resistance of erythrocytes. The icterus index varied between 15 and 25. A qualitative van den Bergh test gave a delayed direct reaction. The urine contained some urobilin, but no bilirubin. During her stay in the hospital she was afebrile and there was some improvement.

The main clinical impression at this time was acquired (Hayem-Widal) type of hemolytic icterus.

Two months later the patient reentered the hospital because of an attack similar to the first. The physical examination gave the same results, except for signs of fluid in the abdomen which proved to be a transudate with a specific gravity of 1.010. A rose bengal test for hepatic function showed 100 per cent retention of the dye. A modified dextrose tolerance test indicated moderate impairment of carbohydrate metabolism with a blood sugar level of 52 mg per hundred cubic centimeters at the end of three hours.

This new evidence of severe hepatic damage was interpreted as favoring a diagnosis of Banti's disease with secondary cirrhosis. For this reason splenectomy was performed. At operation, the liver was found to be very small and contained large nodules of regenerated tissue, some of which were almost pedunculated. Microscopic examination of an excised wedge of hepatic tissue (fig 5) showed fibrous tissue infiltrated with lymphocytes and adenomatous nodules of hepatic cells lacking normal architecture.

The pathologic diagnosis was cirrhosis of the liver, toxic in origin, with secondary splenomegaly.

Since her discharge from the hospital, the patient has been in fairly good condition provided she is relieved every two to three weeks of about 7 liters of ascitic fluid. Seven months after the patient's second hospitalization, both tests for hepatic function were repeated. On this occasion, the rose bengal test showed a retention of 92 per cent of the dye at the end of eight minutes, and 84 per cent at the end of sixteen minutes. The modified dextrose tolerance test gave a normal blood sugar curve with a terminal blood sugar level of 79 mg per hundred cubic centimeters of blood.

COMMENT

The clinical diagnosis in the first reported case was portal (Laennec's) cirrhosis of the liver. Marked retention of rose bengal dye was entirely in keeping with this diagnosis, but the normal response to the modified dextrose tolerance test was contrary to my previous experience with patients having portal cirrhosis. When the patient died the original pathologic diagnosis also was portal cirrhosis. All steps of the modified dextrose tolerance test were retraced, but no mistakes in technique were discovered, and the discrepancy could not be accounted for.

Several months later, the patient in case 2 was seen, and a clinical diagnosis of cholemia due to cirrhosis of undetermined nature was made. The rose bengal test in this case was superfluous because of the presence of deep jaundice, which is always accompanied by retention of the dye roughly in proportion to the degree of jaundice. A modified dextrose tolerance test was performed, and, contrary to expectation, indicated normal carbohydrate metabolism. Postmortem examination revealed subacute atrophy of the liver with regenerative hyperplasia and early toxic cirrhosis.

The appearance of the liver which, as shown in figure 2, consisted mostly of newly regenerated, bile-stained tissue, suggested that the contrast between clinical cholemia and a normal carbohydrate metabolism may be explained on the basis of the new liver cells having no connection with the biliary tree. If this were correct, the liver would be severely handicapped in the performance of its excretory functions. At the same time, the new tissue having an efficient circulation of blood would be capable of performing its metabolic functions and among them those of glycogenesis and glycogenolysis.

Microscopic examination of tissue from various parts of the liver confirmed this hypothesis by showing complete destruction of parenchyma in the red marginal zone (fig 3) and biliary stasis and absence of lobular arrangement in the hyperplastic nodes of regenerated cells (fig 4). The bile-stained appearance of the new hepatic tissue in toxic cirrhosis and the apparent lack of biliary capillaries in the hyperplastic nodules were mentioned by Mallory,⁴ who was the first to describe this type of cirrhosis, ascribing it to repeated attacks of subacute yellow atrophy of the liver. More recently, the same features were emphasized by Pratt and Stengel,⁵ and by Connor.⁶

Since the foregoing observations brought into harmony all clinical and laboratory data in the second case, at first so puzzling, the necropsy material of the first case was reviewed (fig 1) with the result that the pathologic diagnosis was changed from portal to toxic cirrhosis of the liver.

The third patient, who fortunately is still alive, furnished one more aspect of the unfolding panorama of functional hepatic regeneration in toxic cirrhosis. The first clinical diagnosis in this case was acquired hemolytic icterus (Hayem-Widal type), which was later changed to

4 Mallory, F. B. Cirrhosis of the Liver. Five Different Types of Lesions from which It May Arise, *Bull. Johns Hopkins Hosp.* **22**: 69 (March) 1911.

5 Pratt, J. H., and Stengel, A. Toxic Cirrhosis Resulting from Acute Liver Atrophy, *Tr. A. Am. Physicians* **41**: 100 (May) 1926.

6 Connor, C. L. Toxic Cirrhosis of the Liver, *Canad. M. A. J.* **17**: 546 (May) 1927.

Banti's disease The rose bengal test showed complete retention of the dye in the blood stream, indicating total loss of permeability on the part of the liver. On the other hand, the modified dextrose tolerance test indicated only moderate disturbance of carbohydrate metabolism. During operation for removal of the spleen, advanced cirrhosis of the liver was discovered which, with the help of a biopsy specimen from the liver (fig 5) was identified as belonging to the toxic group.

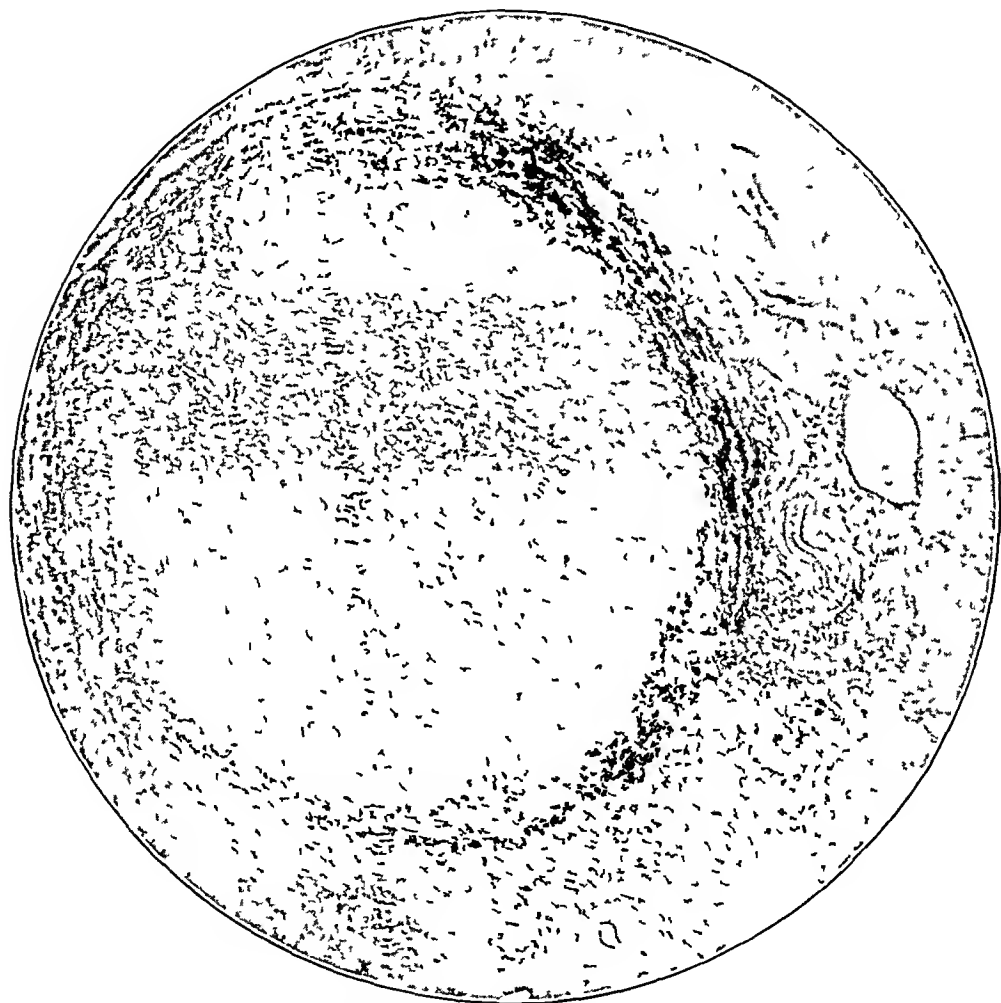


Fig 5 (case 3) —Section of biopsy specimen from the liver showing great loss of hepatic substance around an adenomatoid nodule of hyperplastic cells, $\times 48$

Seven months later both hepatic function tests were repeated. The rose bengal test still showed marked, though not complete, failure in the excretion of dye, but the modified dextrose tolerance test this time gave a normal blood sugar curve. This patient demonstrated that during the acute stage of toxic cirrhosis of the liver, both the excretion of dye and the regulation of the carbohydrate metabolism are impaired, the former much more than the latter probably because regeneration in the

liver is taking place simultaneously with necrosis, though not keeping pace with it. On the contrary, in the chronic stage regeneration of new hepatic cells predominates and the metabolic functions of this organ proceed in a normal manner.

It is significant from the point of view of establishment of proper drainage of bile of the new hepatic tissue that seven months after the acute attack, when sugar metabolism had returned to normal, grave impairment of the excretion of dye, comparable in its severity to that in the two fatal cases, still existed.

Whether excretory channels ever become available to regenerated parenchyma in toxic cirrhosis of the liver is an interesting question that I hope to be able to answer by following the third patient longer. The slight return of the ability to excrete dye observed in this case so far does not prove anything, because it can be accounted for by subsiding inflammation and edema which accompany necrotic processes and which would contribute to retention of dye during the acute stage.

The present work makes possible clinical differentiation between toxic cirrhosis of the liver and a number of other conditions, principally portal cirrhosis, by demonstrating in the former normal carbohydrate metabolism and at the same time marked retention of dye.

The difficulties of diagnosis in this disease are evident. A history of intermittent jaundice appears to be the only differential symptom of value in toxic cirrhosis, and this feature is not a constant manifestation, appearing only once in the three cases here reported. In none of these cases was the diagnosis made clinically, although opinions were given by several competent consultants. The same is true of the cases reported by Connor⁷. Any test, therefore, which will assist in the diagnosis of toxic cirrhosis will probably find a wide field of usefulness in the study of diseases of the liver.

SUMMARY

1 In toxic cirrhosis of the liver, vigorous regeneration of tissue maintains the carbohydrate metabolism-regulating function and probably other metabolic activities of this organ.

2 Owing to a loss of the original structure of the liver in this disease, the new hyperplastic nodules lack connection with bile channels, accounting in this manner for marked impairment in the excretion of dye.

3 This information can be utilized by the clinician for differential diagnosis of toxic cirrhosis of the liver by the use of two suitable tests of hepatic function.

⁷ Connor, C. L. Personal communication.

NORMAL ASYMMETRY AND UNILATERAL HYPERTROPHY¹

GEORGE HALPERIN, M D

CHICAGO

The question of bilateral asymmetry of the human body has been the subject of numerous investigations and researches on the part of anatomists, anthropologists and archeologists of the past century. As a result of exact measurements taken from a great number of cadavers and living subjects, it has been established that the two halves of the body in the human species, as well as in the higher vertebrates, are in reality never symmetrical. This fact being established, a more detailed study of various asymmetries followed.

Meckel¹ was the first anatomist to treat the subject in a scientific manner. Various asymmetries and their physiologic significance were exhaustively treated by von Bardeleben² in a paper presented by him before the Anatomische Gesellschaft in 1909. A French investigator, Richard Liebreich,³ made a most painstaking study of skulls and faces of various races and various periods. In contradistinction to the well-known views of Lombroso and Nordau, Liebreich reached the conclusion that asymmetry of the skull and face is a constant and characteristic feature of the human species. He found that Negroes presented less asymmetry than white persons, and that generally speaking the higher the scale of civilization the more pronounced was the facial asymmetry.

It is now common knowledge that the left cerebral hemisphere, the left half of the skull and the left side of the face are larger than those of the right. The left frontal bone is better developed and projects further forward. The left cheek and the left half of the lower jaw are more prominent. On the other hand, the right halves of the vertebral bodies, as well as the ribs of the right side, are larger than those of the left. In at least 70 per cent of cases, the right half of the sternum is larger than the left. Measurements of the bones of

¹ Submitted for publication, Jan 7, 1931

1 Meckel, J F. Ueber die seitliche Asymmetrie im tierischen Körper, Anatomische physiologische Beobachtungen und Untersuchungen, Halle, Renger, 1822, p 147

2 von Bardeleben, Karl. Ueber bilaterale Asymmetrie beim Menschen und bei höheren Tieren, Verhandl d anat Gesellsch, Jan 23, 1909, Anat Anz **34** 2, 1909

3 Liebreich, Richard. Die Asymmetrie des Gesichtes und ihre Entstehung, Munich, J F Bergmann, 1908

the upper extremities demonstrate that the bones of the right side are somewhat longer and slightly thicker than those of the left. The length of the right upper extremity may exceed that of the left by 1 cm, or even by 2 cm.

The situation is reversed for the lower extremities, the left leg more often being longer and stronger than the right, an instance of crossed asymmetry. Cox⁴ found that in living subjects the difference in the length of the lower extremities amounted to from one eighth to seven eighths of an inch, and that the left extremity was more often the longest. That the pelvis is practically never symmetrical is well known to obstetricians and orthopedists.

The right ear and the right eye are more often a few millimeters, and even a centimeter, higher than the left. The two nipples are never at the same level or at the same distance from the median line. The right nipple is always a little higher. The two breasts are never at the same level, the left usually being the larger. The so-called median line, because of irregularities in the size of the two halves of the neck and the thorax, is in reality never in that position. The sculptors of the best periods of ancient Greece and Rome were apparently aware of this natural asymmetry. The heads and bodies of their statues were distinctly asymmetrical, which suggests that they modeled after living subjects rather than after some formula. The anatomists did not become aware of this fact until a century ago.

From a physiologic standpoint the most interesting asymmetries are those of the skull and face and of the preponderant right-handedness.

So far the discussion has been concerned with what may be termed normal asymmetry. It is not usually apparent and must be established by exact measurements. On the other hand, gross asymmetry, which is at once perceptible to the eye, even of any part, is rare, a decided inequality of the two halves is exceedingly rare. It is referred to in the literature as unilateral hypertrophy, hemihypertrophy, congenital hemihypertrophy, hemimacrosomia and partial gigantism. It constitutes the rarest of all developmental anomalies and has given rise to much speculation as to its etiology. The enlargement is more than hypertrophy, it really amounts to mild gigantism. In more than half the cases, along with the anomaly of growth, there are other congenital defects and degenerative stigmas, such as telangiectases, the early appearance of varicose veins, thickening of the skin, syndactylism, clubbed feet and mental defect.

4 Cox, W. C. On the Want of Symmetry in the Length of Opposite Sides of Persons Who Have Never Been the Subject of Disease or Injury to Their Lower Extremities, *Am J M Sc* 69 438, 1875.

AUTHOR'S CASE

History—The patient, aged 23, was admitted to the surgical service of Cook County Hospital on Aug 5, 1930, with a condition diagnosed as bleeding hemorrhoids. He was born in Italy. His mother had noted his asymmetry shortly after birth. There were six brothers and two sisters, all of whom did not present abnormalities. The mother and father were normal. The family history was irrelevant. The patient remembered having had scarlet fever during his childhood. At the age of 16 he had noticed varicose enlargements on the right leg. At the age of 18½ he was operated on for varicose veins of the right leg. Two years later he had noticed the appearance of new varices on the right leg and thigh. The extremity began to increase in size. At about the same time epileptic fits developed. The attacks were always nocturnal and were not accompanied



Fig 1 —The patient's hands, showing the gigantic proportions of the left one

by involuntary defecation or urination. His body was well developed. He was a laborer and had always enjoyed good health. He was not married, but his libido and potency were normal.

Physical Examination—The patient presented a striking asymmetry, the left side being markedly larger than the right. The crown on the left side was higher, and the forehead projected further forward. The left cheek, nostril, lip and ear were larger than those of the opposite side. The median raphe of the face was displaced to the right side. The left half of the jaw was longer and more rounded and projected farther forward. The tongue consisted of a delicate right half and a much larger, thicker and longer left half. The left tonsil was larger than the right.

The left upper extremity was longer and larger than the right. The difference in the size of the two hands was striking. He could lift more with the left though he was right-handed. The left hand, shown in figures 1 and 2, was of

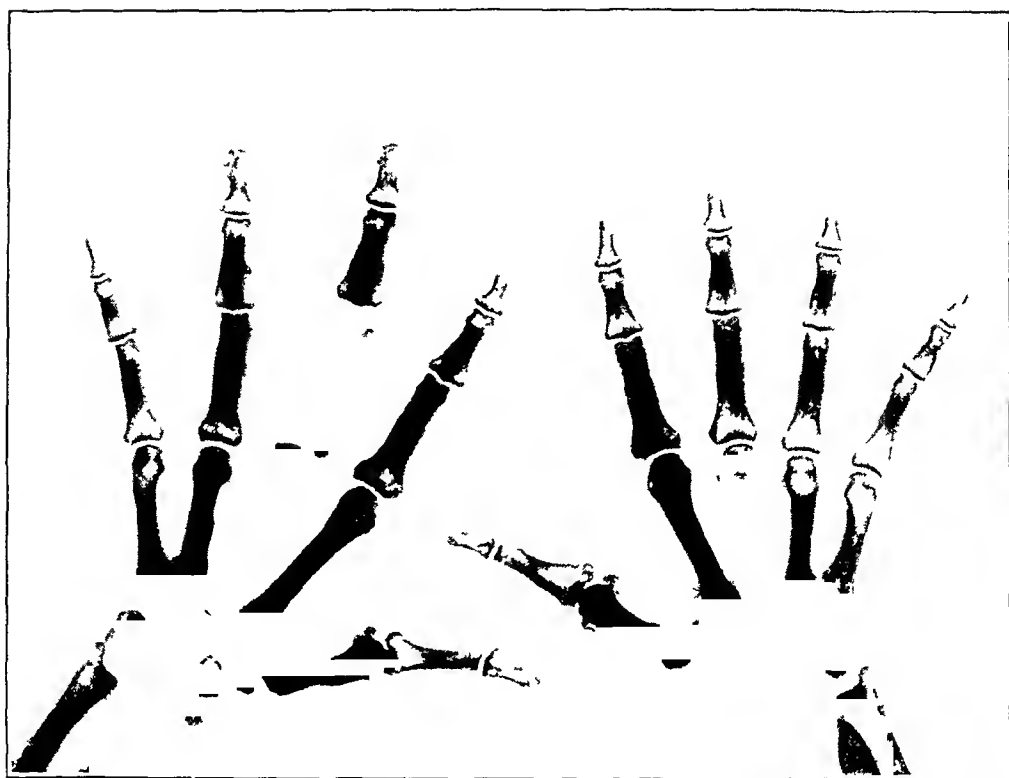


Fig 2—Roentgenogram of the patient's hands, showing the asymmetry

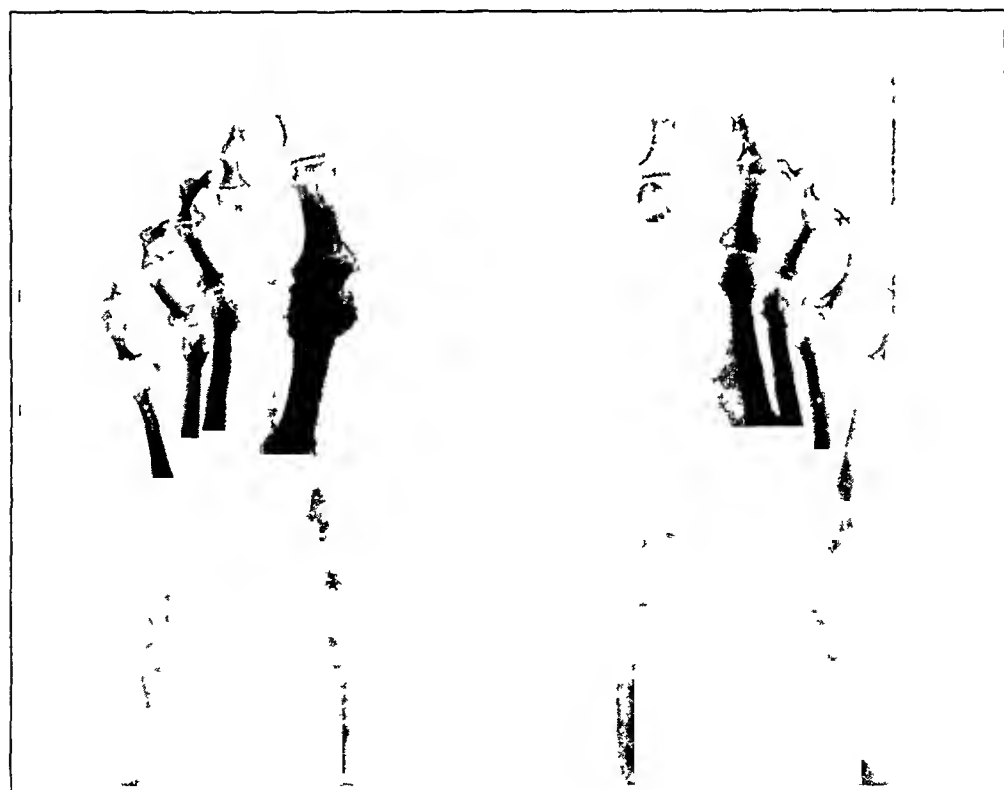


Fig 3—Roentgenogram of the patient's feet

gigantic proportions With the patient lying down, it was at once evident that the left lower extremity was longer than the right Both feet were unusually large The right was much thicker than the left, however, this was apparently due to edema caused by enormous varices Examination of the accompanying photographs gives the impression that the man was formed by the union of two halves from two persons of different size and length

In addition, a supernumerary nipple was noted 6 cm below the right nipple Scattered over the skin of the abdomen, both lower extremities and the entire back were small and large patches of portwine-stained telangiectases There was

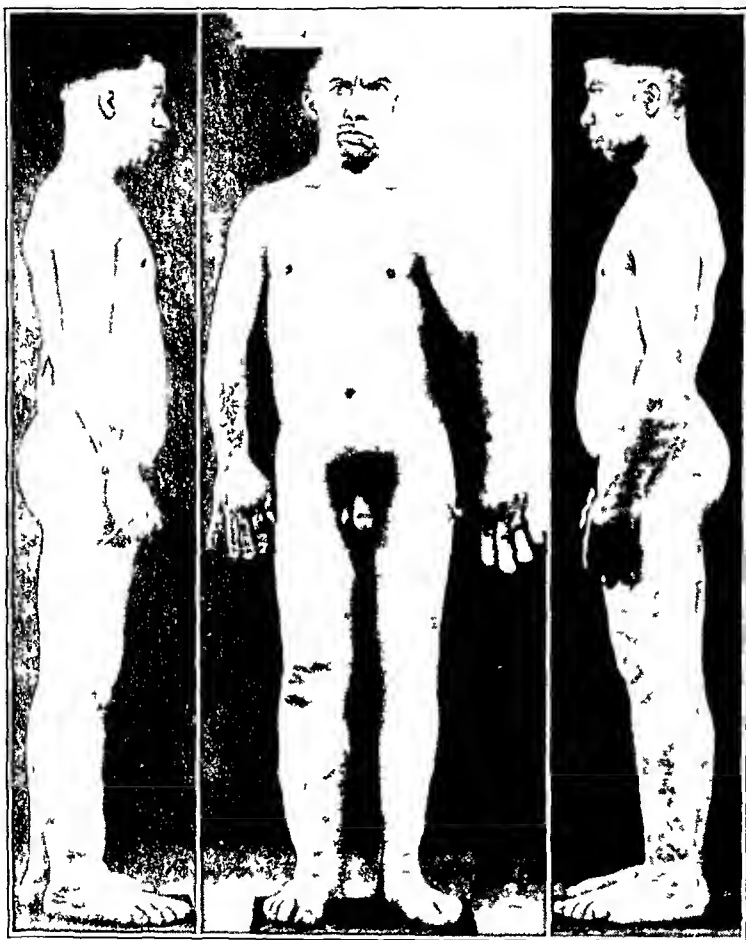


Fig 4—Appearance of the patient

a long operative scar on the inner surface of the right thigh, and two longer scars on the leg The right extremity also presented unusually large varices The genitalia were well developed, the left scrotal sac hanging much lower than the right

Roentgen examination of the skull revealed a perfectly normal, rather small, well outlined sella turcica with normal clinoid processes

The blood pressure on the right side was 100 systolic and 70 diastolic, on the left, 108 systolic and 80 diastolic The mentality was normal

Anthropometric Measurements—The upper extremities, from the tip of the acromion to the styloid process of the radius, measured right, 52 cm, left, 56 cm

The circumference of the thorax at the level of the nipples measured right half, 42 cm, left half, 46 cm

The lower extremities, from the superior anterior iliac spine to the inferior aspect of the internal malleolus, right, 85.5 cm, left, 89.5 cm

ETIOLOGY OF CONGENITAL HEMIHYPERTROPHY

That the incidence of this anomaly is extremely rare can be seen from a survey of the literature. In 1869, Trélat and Monod,⁵ in an exhaustive paper, were able to collect eleven cases. Gesell,⁶ in a careful review of the literature to 1921, gathered forty cases of total hemihypertrophy. In 1927, he was able to add thirteen to this number, making a total of fifty-three cases. Analysis of these cases reveals a slight preponderance of males and a slight preference for the right side. All cases were of congenital origin, the anomaly having been noted immediately or shortly after birth. Heredity appears to have no part in the production of the anomaly, to the contrary, the absence of hereditary influences is conspicuous.

Information gained from a few postmortem examinations is more or less negative. Cagliati,⁷ in a postmortem study of a typical case in a child 2½ years of age, reported the absence of any abnormality in the nervous system. The changes consisted of a hypertrophy of the connective tissues, the bones and the blood vessels of the affected side. Practically, the same findings were reported by Arnheim,⁸ Hornstein⁹ and Hoffman¹⁰. The blood vessels of the involved side were larger and showed particularly hypertrophy of the tunica media and the tunica intima. Cagliati concluded that the condition is a unilateral hypertrophy of unknown cause, involving the tissues derived from the mesenchymal layer. The enlargement of the blood vessels and the frequent occurrence of vascular abnormalities, such as nevi and telangiectasias, led some investigators to believe in a vascular origin of the disturbance. The theory is inadequate, because only about half of the cases show these vascular abnormalities, and the latter are not

5 Trélat, U., and Monod, A. De l'hypertrophie unilatérale partielle ou totale du corps, *Arch gén de méd* **13** 536, 1869

6 Gesell, Arnold. Hemihypertrophy and Mental Defect, *Arch Neurol & Psychiat* **6** 400 (Oct) 1921, Hemihypertrophy and Twinning, *Am J M Sc* **173** 542, 1927

7 Cagliati, Luigi. Klinischer und pathologischer Beitrag zum Studien der halbseitigen Hypertrophie, *Deutsche Ztschr f Nervenhe* **32** 282, 1907

8 Arnheim, G. Ueber einen Fall von congenitalen halbseitiger Hypertrophie mit angeborenen Bronchiectasien, *Virchows Arch f path Anat* **154** 300, 1898

9 Hornstein, S. Ein Fall von halbseitigem Riesenwuchses, *Virchows Arch f path Anat* **133** 440, 1893

10 Hoffman, Max. Zur Pathologie des angeborenen, partiellen Riesenwuchses, *Beitr z klin Chir* **43** 391, 1906

necessarily confined to the hypertrophied side. It is more probable that the blood vessels share in the general hypertrophy.

In a case reported by Hutchison,¹¹ with postmortem observations by Turnbull, the latter concluded that the enlargement was caused by the obvious hypertrophy of the right suprarenal gland, the left apparently being of normal size. He also thought that the right testis was abnormally large. It is apparent that not much light has been shed by postmortem studies.

Gesell's speculations are interesting. He considered hemihypertrophy an atypical or imperfect form of twinning. By twinning is understood the production of equivalent structures by division. The tendency to bilateral equivalence, to symmetry or to mirror imaging is one of the fundamental laws in biology. Hemihypertrophy appears to be "a profound inaccuracy in the natural process of developmental duplicity." Gesell defined it as a mild unilateral gigantism of a person whose lesser somatic half is normal.

The damage or some abnormal stimulus to one half of the soma must take place early in embryonic existence. Important contributions to the solution of this biologic riddle should come from the fields of experimental embryology and teratology.

An attempt has not been made to review all the papers published or to mention all of the cases, since that has already been done. I wish, however, to add two cases to the list collected by Gesell. They have not been mentioned in any of the important contributions, because they were published under the title of "Asymmetry" and not of "Hypertrophy." I have reference to the cases of Humphrey¹² and Wachsnier¹³.

25 East Washington Street

¹¹ Hutchison, Robert. Hemihypertrophy with Postmortem, *Brit J Child Dis* **13** 233, 1916.

¹² Humphrey, G. M. Asymmetry of the Two Halves of the Body, *J Anat & Physiol* **6** 226 (Nov.) 1869.

¹³ Wachsnier Fritz. Zur Kenntnis der bilateralen Asymmetrie des menschlichen Körpers, *Berl klin Wchnschr* **51** 1953, 1914.

ISOLATED CONGENITAL DEXTROCARDIA

REPORT OF TWO CASES WITH UNUSUAL ELECTROCARDIOGRAPHIC
FINDINGS, ANATOMIC, CLINICAL, ROENTGENOLOGIC AND
ELECTROCARDIOGRAPHIC STUDIES OF THE CASES
REPORTED IN THE LITERATURE^{*}

S S LICHTMAN, M D

NEW YORK

Introduction

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Report of Cases Personally Observed

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Situs Inversus of Viscera with Situs Solitus of the Heart

Summary

INTRODUCTION

While cases of total situs inversus have been recognized since antiquity, isolated dextrocardia has been noted only in the past two centuries. Despite its comparative rarity, an extensive casuistic literature exists. This type of dextrocardia merits a comprehensive study, since it involves one of the most complex phases of cardiology.

The early contributions to the literature are mainly anatomic, the clinical reports being inadequate in the light of modern cardiologic methods. The roentgenographic and electrocardiographic methods of examination have added precision to the clinical diagnosis of this anomaly. The roentgenographic method permits the differentiation of the congenital from the acquired types of dextroposition of the heart,

^{*} Submitted for publication, Dec 6, 1930

^{*} From the Medical Department of the Mount Sinai Hospital New York, service of Dr. George Baehr

and total situs inversus from the isolated type. The electrocardiographic method yields information concerning the inner topography of the heart. Despite the increasing number of case reports, there are four that have been completely studied (Bahn, Pol, Plumier-Clermont, Biedermann, Rosler, Spitzer). The present study, comprising two personal observations and a critical analysis of the literature, aims to elucidate the anatomic, clinical, electrocardiographic and roentgenographic observations in this type of dextrocardia.

DEFINITION

By the term dextrocardia should be designated only those cases in which the heart, in its own development independent of disease and anomaly in surrounding structures, assumes a position in the right side of the thorax with the apex pointing to the right. Its congenital nature is obviously assumed. "Dextroversio cordis" should, in my opinion, characterize those cases in which the displacement of the heart is dependent on a congenital or acquired extrinsic cause*. Differences in definition and contradictory concepts of the different forms of dextrocardia prevail in the literature. Nearest to the present interpretation is that of the French school (Clerc and Bobrie, Vaquez and Donzelot and others), which recognizes as dextrocardia or "dextrocardie" every primary congenital displacement of the long axis of the heart to the right, as opposed to "dextroversio cordis" applied to every acquired displacement of the heart to the right side with the apex to the left due to extracardiac causes. Vaquez and Donzelot recognized a congenital dextroversion.

The "ideal" dextrocardia is defined by Foggie as the mirror-image of the normal heart as it is found in situs inversus. The term dextrocardia is used by some German writers (Herxheimer, Monckeberg, Peinkopf) to denote only the type associated with inversion of the chambers of the heart, while the terms "dextropositio cordis" (Pernkopf) and "dextroversio cordis" (Palttauf, Pal, Monckeberg, Romberg, Jones, Vaquez and Donzelot and others) are reserved for the right-sided heart with normal relationship of its chambers—the former term for displacement of the heart in toto, the latter for the mirror-image displacement of its axis. The heart with normal architecture is, according to Nagel, a "genuine dextrocardia". Kundrat reserved the term, "transpositio cordis" for proved cases of transposition of the heart or

* My definition allows for Spitzer's new concept of the term "dextroversio". According to him, its characteristic is the inverse direction of the axis which is not the result of mirror-picture architecture of the heart but of gross pathologic causes. Some cases (Rosler's case 1) of "larvierte" inversion must be taken from the group of dextroversions and included in the group of dextrocardias (when the apex of the heart lies to the right).

its individual parts and "dextrocardia" for unproved cases of right-sided heart. In its broadest sense the term dextrocardia is used to include every dextroposition of the heart, acquired or congenital (Mandelstamm and Reinberg). Rosler likewise in this liberal sense stated that the term should not convey more than the information that the greater part of the heart lies in the right side of the chest.

The merit of the terms as defined by me lies in the differentiation of the primary idiopathic type from the secondary type of cardiac dextroposition on a purely embryologic basis, eliminating from the category of dextroversio cordis those cases of primary dextrocardia with normal relationship of the chambers, the mechanism of whose pathogenesis is obviously different from those dependent on extracardiac causes.

By the term "isolated" dextrocardia is meant heterotaxia of the heart alone with normal position of all other viscera (Foggie, Geoffrey St Hilaire). Hitherto a difference in concept has existed, the term "pure" dextrocardia having been used synonymously with "isolated" (Vaquez and Donzelot, Clerc and Bobrie, Nagel, Pal). By others, "pure" has been employed to signify an "uncomplicated" mirror image dextrocardia (Blumenfeldt). Graanboom used pure in the sense of an uncomplicated isolated dextrocardia.

Dextrocardias are considered "complicated" or "uncomplicated," depending on whether cardiac malformations accompany the anomalous position of the heart. The proposal to limit the term "isolated" to "uncomplicated pure" cases (Clerc and Bobrie, Vaquez and Donzelot) is not warranted.

REPORT OF CASES PERSONALLY OBSERVED

CASE 1—*History*—T. R., aged 19 years, single, a telephone operator, was admitted to the Mount Sinai Hospital on May 25, 1928, to the dermatological service of Dr. Hermann Goldenberg, who gave me permission to report the case. The presence of the dextrocardia was discovered by the ward physician, Dr. L. R. Tuchman, in the course of a routine examination. The patient had been referred to the hospital for the treatment of an eruption on her face and arms of three years' duration. Her father was alive and well, her mother died of influenza in 1918. A sister and brother were well. So far as she knew, no member of her family suffered from cardiac trouble or anomaly of the position of the heart. There was no history of consanguineous marriage in the family. As a child she suffered from scarlet fever and measles. Six years before admission to the hospital, her tonsils were removed. There was no previous history of pleurisy or pneumonia. She had frequent colds in the winter. One year before admission, she lost her voice for six months due to laryngitis. She had never had hemoptysis. She had frequent headaches at the end of the working day. At the age of 4, she became aware that her heart beat on the right side. At the age of 8, she was restricted in her activities because of pain in the cardiac region on exertion. Cyanosis was not noticed at this time, but the fingers sometimes became blue, the lips were not noted. Ordinarily she had slight dyspnea on exertion. There was no history of rheumatic fever, pains in the muscles and joints or chorea.

There had never been any swelling of the lower extremities. The menses, which began at 13, were regular with no dysmenorrhea. The patient was moderately obstipated. Three years before admission, an eruption appeared on the dorsum of the right arm up to the level of the elbow. Despite topical and roentgen treatment for a year and a half, the lesion persisted. Then the face became involved, especially the cheeks, forehead and ears. The lesions were better in summer than in winter.

Physical Examination—The stature and weight of the patient were normal for her age. On her face were impetiginous areas, crusted over with yellowish exudate and with an inflammatory reddened base. The forehead was covered with lesions similar to those of the face except that there was less exudate. The lips were reddish in color, not blue or pale. There was no adenopathy. Intranasal examination indicated the presence of bilateral disease of the ethmoid. Examination of the lungs revealed no abnormalities. There were no râles at the bases of the lungs.

Heart The apex beat was in the fifth intercostal space, 6 cm to the right of the midline. The right border of cardiac fulness was 3 cm to the right of the midline in the second space, 5 cm in the third space and 5 cm in the fourth space. The left border was inside the left sternal margin in the second and third intercostal spaces and just to the left of the sternal margin in the fourth intercostal space. The heart sounds were of good quality. There was a short rasping systolic murmur heard over the entire precordium. No thrill was felt. There was a pulsation systolic in time in the third and fourth right intercostal spaces near the sternum. There was a rough systolic murmur in this area especially, besides the one over the apical region. The second sound was short and snapping. The cardiac sounds were also audible to the left of the sternum, but they were not as loud.

Examination of the extremities showed moderate clubbing of the fingers. There was no cyanosis and no edema of the extremities.

Abdomen The liver was not palpable. There was dulness in the right hypochondriac region. A tympanic note was heard in the left upper quadrant. The abdominal aorta pulsated to the left of the vertebral column.

Skeletal There was slight scoliosis of the thoracic spine.

Laboratory Examination—The Wassermann reaction of the blood was negative. Analysis of the blood showed urea, 13 mg, cholesterol, 160 mg, and sugar, 73 mg per hundred cubic centimeters of blood. The basal metabolic rate was minus 12 and minus 15 per cent.

Roentgenographic Examination—Fluoroscopy was done on Nov. 30, 1928. The right border of the heart was rounded, but the apex was not definitely found. The aortic arch was partially to the left of the sternum. The retrocardiac space was seen in the second oblique position. The arch of the aorta was visualized in the right first oblique position, corroborated in the posterior anterior view. The liver and stomach were in their usual position (fluid level and carbon dioxide inflation by compound effervescing powder, U S P).

X-Ray Plate of Chest The heart (fig 1) was completely transposed to the right side of the chest. The right border of the heart was rounded. There was no abnormality in the thoracic wall, other viscera or the pulmonary fields to account for the abnormal position of the heart. The aortic arch crossed the left bronchus. The right leaf of the diaphragm was lower than the left.

Electrocardiographic Examination—The tracing (fig 2) showed a very low P wave inversion of the T wave and an upright QRS complex in lead I. T2 was

slightly inverted Leads II and III were not interchanged There was no ventricular predominance There was normal sinus rhythm

Diagnosis—Isolated mirror-picture dextrocardia, defect of the interventricular septum, generalized neurodermatitis and bilateral ethmoiditis were diagnosed

Course—The patient continues to work as a telephone operator and has been well except for the condition of her skin, for the treatment of which she returned to the hospital in June, 1929 At that time the foregoing diagnosis were reaffirmed The cardiac symptoms remained unchanged

Comment—The congenital nature of this case is beyond doubt, the dextrocardia was recognized at the age of 4, and some transitory limi-



Fig 1 (case 1) —Roentgenogram of chest showing position of the heart

tation of physical activities at the age of 9 due to cardiac symptoms The patient now works and lives a normal life The dextrocardia was recognized incidentally, the patient seeking relief for a cutaneous disease The associated cardiac malformation is likewise undoubtedly congenital in nature The absence of frank cyanosis and a thrill argue against the presence of a pulmonary stenosis The aorta crosses the left bronchus and descends on the left side of the vertebral column The abdominal organs occupy their normal position The roentgenogram of the chest shows clear, pulmonary fields The right leaf of the diaphragm is lower than the left The very low P wave and the inversion of the T wave in the first lead of the electrocardiogram suggests the possibility of inversion of the chambers of the heart The upright QRS

complex in lead I would indicate that the greatly hypertrophied transposed "right" ventricle, now on the left side, distorted the electrocardiogram. This view is supported by the electrocardiographic and anatomic evidence in the case of Abbott and Moffatt, the electrocardiogram and roentgenogram of which are here reproduced (figs 3 and 4). In this case a mirror-picture dextrocardia occurring in a partial heterotaxia was found, and was diagnosed *intra vitam* by the roentgenogram and the electrocardiogram. The P and T waves in lead I were inverted, and the QRS was upright instead of the familiar inversion of all the

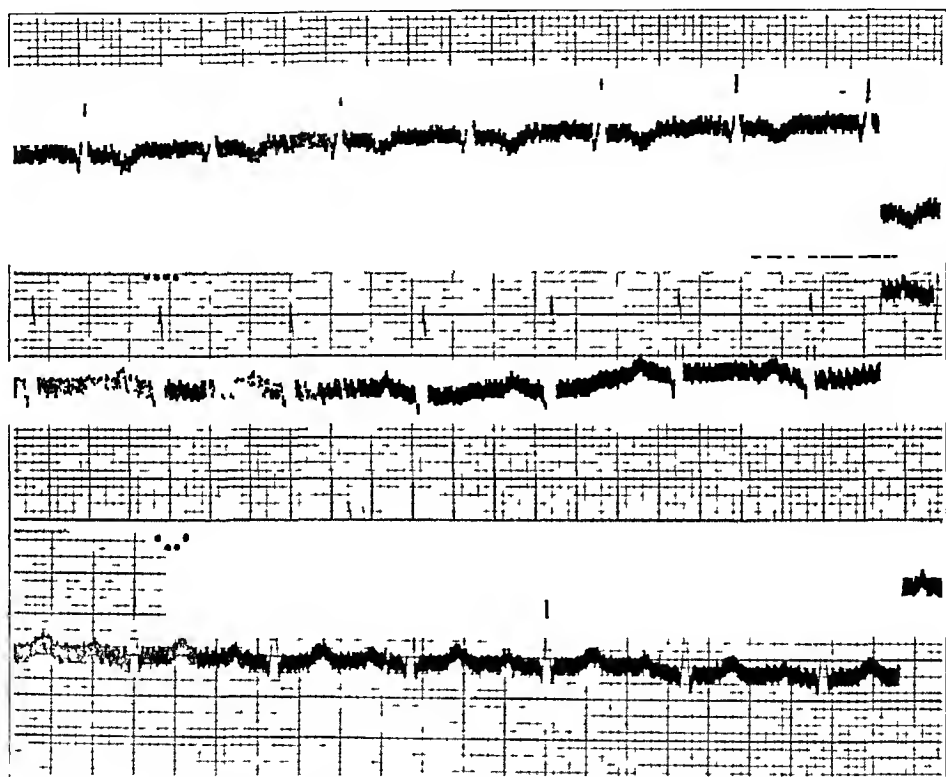


Fig 2 (case 1) —Leads I, II, III from above downward

main deflections always found in this lead in cases of uncomplicated mirror-picture dextrocardia. Anatomically, a markedly hypertrophied transposed "right" ventricle and an aplastic transposed "left" ventricle were found. My case, that of Abbott and Moffatt, the following case and other cases to be cited subsequently (cases under "Unusual Findings in Dextrocardia," second installment of article) stress a new phase of the interpretation of the electrocardiogram in cardiac conditions associated with simultaneous displacement of the cardiac axis, alteration of the inner topography of the heart and cardiac malformation and disease.

CASE 2—History—A H., aged 43, married, an upholsterer, was admitted to the outpatient department of the Mount Sinai Hospital on Oct 17, 1927, where I observed him. He complained of pain on urination and occasionally inability to

pass urine. He had a daughter 19 years old (right-handed) and another 6 years old (left-handed), both were well, and were not known to have malposition of the heart. A son of 14 years (right-handed) was found to have a normally situated heart. The patient's wife was well, and her heart was in its normal position. There was no family history of consanguineous marriage. The patient suffered the usual diseases of childhood. There was no history of pleurisy or pneumonia. He always enjoyed good health. Three years before admission, he had attacks of pain in the left loin. He was unable to pass urine and had to be catheterized. He had never had influenza. He had never noted or been informed by a physician of displacement of his heart. He was a heavy smoker and did not drink alcoholic beverages. For three years before admission he had had a cough now and then,



Fig 3—Roentgenogram of chest in Abbott and Moffatt's case 2 (Published for the first time, with permission of the authors)

with dark scant expectoration, occasionally blood-streaked. He had noticed shortness of breath on walking rapidly or climbing stairs. At no time had he suffered an attack of syncope. Three weeks before admission he again noted difficulty in urination accompanied by an attack of severe pain in the left side. He was catheterized. The urine contained blood. He passed small amounts of urine containing blood with great pain.

Physical Examination—The patient was a robust man of medium height weighing 177 pounds (80.3 Kg). He had a peculiar pallor, but no evidence of cyanosis. His eyes reacted to light and accommodation. The tonsils were markedly hypertrophied. His neck was short and stout. He was hyposensitive to pain (Libman's test). He was right-handed.

Chest The thorax was symmetrical, resonance was normal throughout. Tactile fremitus was more marked over the right side of the chest. The expiratory phase of respiration was prolonged. There were numerous musical râles throughout both sides of the chest. There were no moist râles to be heard at both pulmonary bases.

Heart An area of pulsation was visible in the right sixth intercostal space 10 cm from the midline, and the apex beat was palpable in this region. There was no pulsation visible in the left side of the thorax. On percussion, the heart was found to be enlarged. The major portion of the area of cardiac dulness was in the right side of the chest, although a portion of the heart was found to the

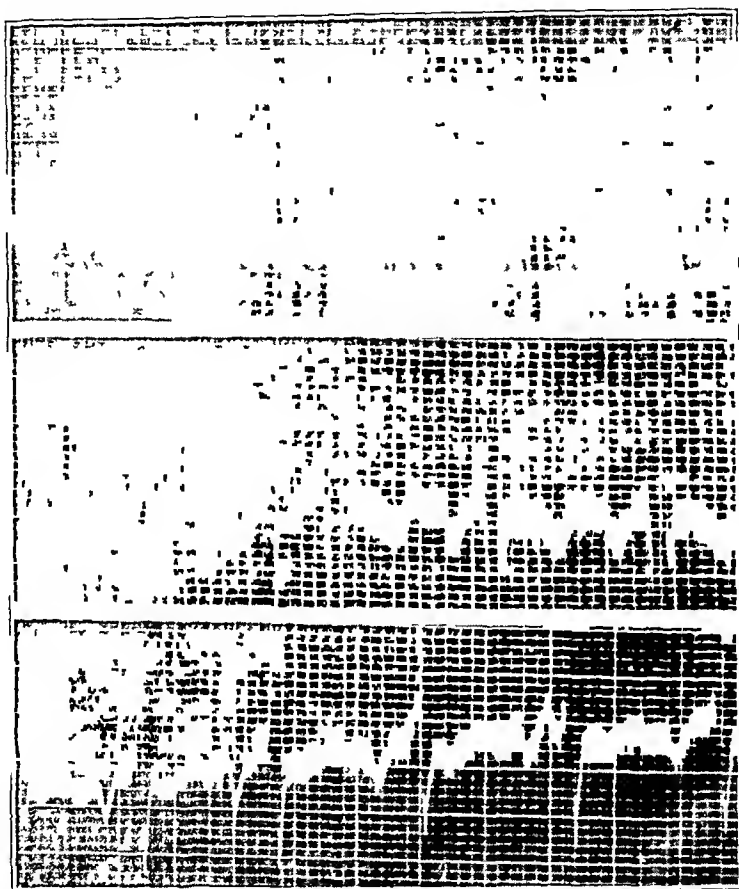


Fig 4—Electrocardiogram in case 2 of Abbott and Moffatt. Lead I, P and T inverted, upright, “Q” unusually deep, leads II, P and T inverted, upright, “Q” unusually deep, lead III, P diphasic, upright, T upright, rhythm regular, normal conduction. At necropsy, a markedly hypertrophied transposed “right” ventricle and an aplastic transposed “left” ventricle were found. (Published for the first time, with permission of the authors.)

left of the sternum. In the second intercostal space, the heart percussed 6 cm to the right and left of the midsternal line, in the third, 8 cm to the right and 7 cm to the left, in the fourth, 10 cm to the right and 7 cm to the left, and in the sixth intercostal space 13 cm to the right of the midline. Below, the area of cardiac dulness was continuous with the area of hepatic dulness.

The heart sounds were best heard in the right fifth and sixth spaces, although they were also heard faintly in the same spaces just to the left of the sternum. A

soft systolic murmur was heard in the fifth and sixth spaces to the right and left of the sternum. There was no palpable thrill. The second sound in the second right intercostal space was louder than that in the corresponding second left intercostal space. When the patient was shifted, the area of cardiac dulness moved to the right or left.

The radial pulse was regular, the rate varying between 45 and 58 beats per minute on five different examinations. There was no deficit of the pulse. In the right arm, the blood pressure was 135 systolic and 80 diastolic, and in the left, 125 systolic and 60 diastolic. There was only slight clubbing of the fingers.

Abdomen. The liver was palpable one fingerbreadth below the right costal margin. The abdominal aorta was not palpable. The left testicle was lower than the right.

Laboratory Examinations.—Urinalysis showed the presence of albumin, numerous red blood cells, a moderate number of white blood cells and an occasional hyaline cast. The sputum contained no tubercle bacilli.

Röntgenographic Examination.—Fluoroscopy was done. The examination of the chest was interpreted as follows. The two main cardiac contours were the ventricles in their normal relationship, except that the right was huge and the left hypoplastic, the aorta was anomalous and small, the pulsations of the right and left cardiac borders were synchronous and regular, the auricles could not be identified (important in view of the presence of auricular fibrillation). The esophagus as outlined by barium sulphate appeared to be in its normal position and relation to the aorta (persistent right aortic arch ruled out). In the right oblique position, the retrocardiac space was not visualized, in the left oblique, it was, although in this view the arch of the aorta could not be definitely outlined. The arch of the aorta was not visualized in the right oblique position either. A vertical shadow above the left contour of the heart was considered as the descending aorta. A shadow at the left leaf of the diaphragm adjoining the left cardiac border was not visualized. The diaphragm moved freely, the right leaf being definitely lower than the left. A barium sulphate meal showed the stomach and duodenum to be normal in position. The liver was in its normal position.

X-Ray Plate. A teleoroentgenogram (fig 5) showed the heart to be enlarged and to be situated almost entirely in the right side of the thorax except for a small portion to the left. In contour, the heart was in mirror-image position to what it would be in the normal subject with definite hypertrophy of the ventricle represented by the right main cardiac contour and that portion immediately above, which in a transposed normal heart would represent the left auricle. The pulmonary artery was now visualized. The arch of the aorta crossed the left bronchus and descended on the left side of the vertebral column. There were some infiltrations in both bases of the lungs probably due to long-standing congestion or bronchiectasis. Dr. Harry Wessler assisted in the interpretation of the roentgenogram. Examination of the urinary tract showed the presence of calculi in the region of both kidneys and one in the lower end of the left ureter about 2 inches above the vesical orifice.

Electrocardiographic Examination.—The electrocardiogram (fig 6) showed ventricular rates of 45, 55 and 52, respectively Nov 2, 1927, Dec 15, 1927, and May 16, 1930, regular in leads I and II and slightly irregular in III. Auricular fibrillation was noted. In lead I, QRS was upright and T inverted. QRS in leads II and III was upright. The T waves were opposite the main deflections in all leads (ventricular complexes were large and diphasic). The QRS interval mea-

sured 012 of a second Leads II and III were not interchanged Drs B S Oppenheimer, M A Rothschild, Hubert Mann and I R Roth aided in the interpretation of the electrocardiogram

Polygraphic Tracing—The polygram made by Dr Hermann Mond showed a venous pulse characteristic of auricular fibrillation The A wave was missing, and a number of small irregular waves were visualized, "fibrillation waves" The systolic collapse of the vein was well marked There was no sign of a tricuspid lesion The arterial pulse showed no abnormality

Diagnosis—Dextrocardia without situs inversus of the ventricles, interventricular septal defect, anomalous position of the great vessels with normal relationship to respective ventricles, auricular fibrillation, congenital complete heart block,

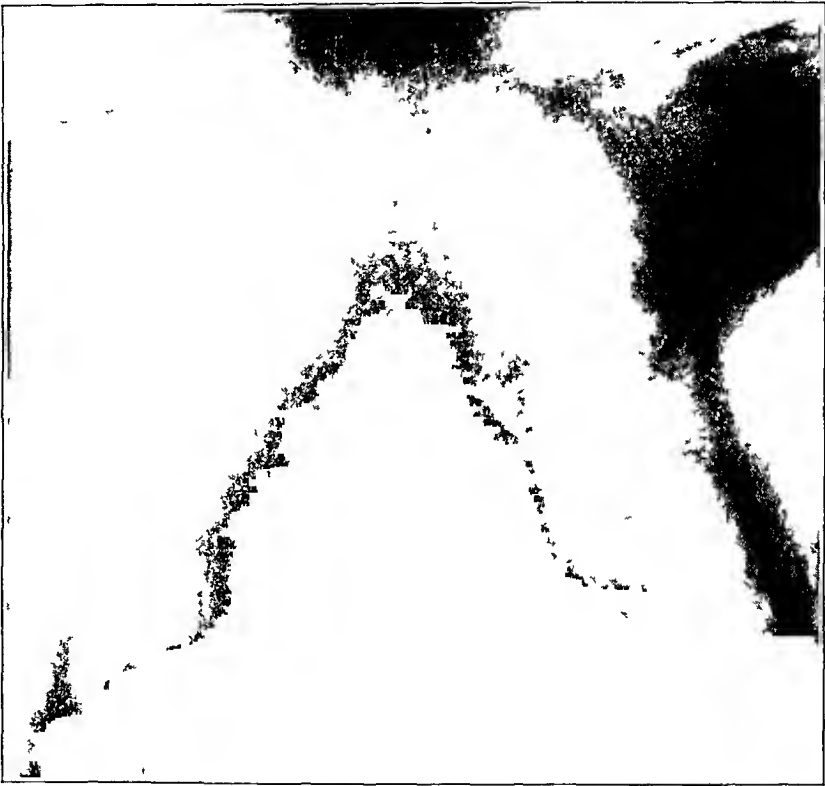


Fig 5 (case 2)—Roentgenogram of chest showing position of the heart

bradycardia (idioventricular rhythm), bronchiectasis (?) and renal and ureteral (left) calculi were diagnosed

Course—The patient has been under observation for two years, during which time there has been no change in his physical condition He works regularly and strenuously The cardiac symptoms remain unchanged There is no evidence of cyanosis or increasing shortness of breath

Comment—The interpretation of case 2 involves a more difficult problem While the dextrocardia was recognized late in life, no etiologic factor can be found to explain the dextroposition other than its congenital nature The absence of cyanosis, the age and physical examination of the patient would indicate that the associated malformation does

not seriously affect the physiology of the heart. Roentgenographic examination shows no cause of traction or of displacement of the heart. The right leaf of the diaphragm is lower than the left, the abdominal organs are in their normal position. In this case as in case 1, the cardiac symptoms were incidental, the patient seeking relief for renal colic. This patient also carries on his occupation, which is strenuous. The roentgenographic evidence of long-standing congestion of the lungs, the symptom-free auricular fibrillation recognized by the electrocardiogram and the venous tracing, a persistent bradycardia without spontaneous syncopal crises and electrocardiographic evidence of complete heart block and idioventricular rhythm with no history of an episode pointing to

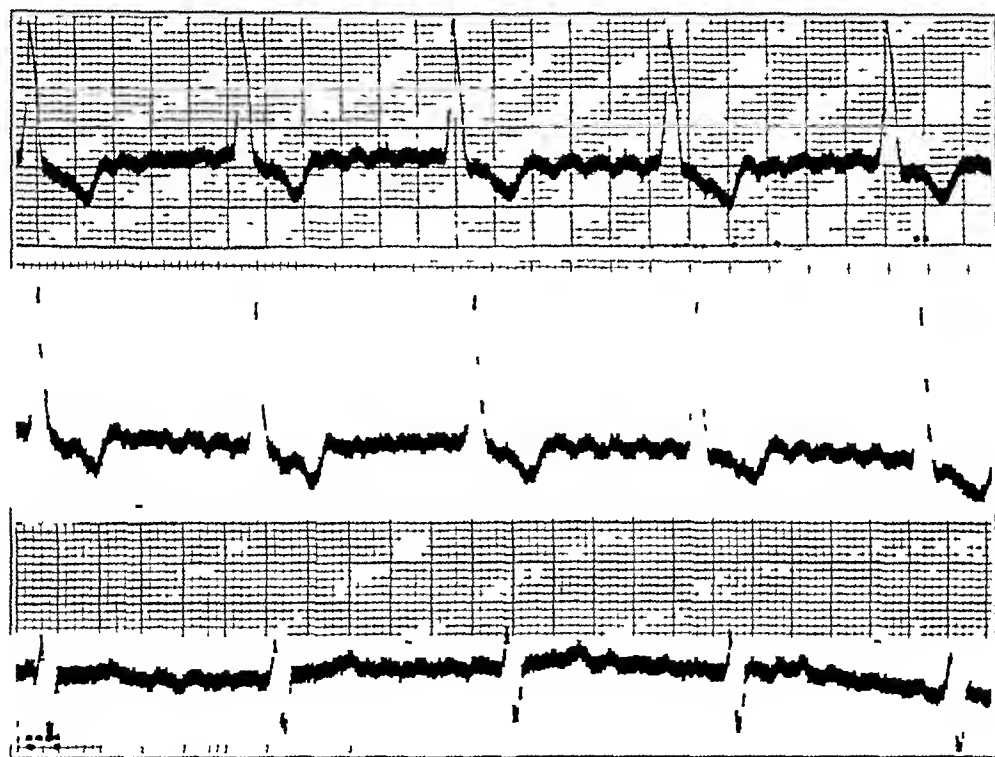


Fig 6 (case 2) —Leads I, II, III, from above downward

disease of the coronary artery in a man only 43 years old with dextrocardia would suggest that the electrocardiographic evidence of both auricular fibrillation and conduction defect are more logically explained as the results of a congenital lesion than an acquired lesion on the basis of disease of the coronary artery.

The persistent regular bradycardia in the presence of auricular fibrillation points to the presence of a block in the main stem of the bundle of His probably associated with the septal defect.

The occurrence of partial heart block in association with congenital cardiac disease, especially defects of the septal and auriculoventricular nodes, was reported by Wilson and Grant (1925) in a child of 14 months in whom pulmonary atresia and complete absence of the interventricular

septum was found. They found in the literature 17 clinical cases of complete and partial heart block of congenital origin and in another case the condition was found post mortem (Storch). The observations of Keith, Monckeberg, Carter and Howland, and Romberg and White indicate that the position of the auriculoventricular bundle on the upper border of the interventricular septum or on the posterior wall of the heart, respectively, is the usual one in hearts in which the septum is partially or totally deficient. In the heart described by Mann and examined microscopically by Monckeberg, the auriculoventricular system was found on the surface of a muscular prominence on the posterior wall of the common ventricle (case of *cor trilobular biatrium*) as in Wilson and Grant's case. Additional cases of congenital origin have been recorded recently by Aylward (2 cases), and Lampard, Fleming and Stevenson (1928) reported 2 cases, 1 partial and the other complete with patent intra-ventricular septum and malformation of the auriculoventricular bundle.

Josué described a case of pulmonary stenosis with intraventricular communication and "allodromic" due to destruction of the terminal left branch of the bundle of His. The electrocardiogram showed delayed conduction, notching of R_{III} opposite deflection of T in leads I and III (upward in I, downward in III) and right ventricular predominance. He maintained (concurring with observations of Keith, Sapegno, Monckeberg, Laubry and Pezzi, and Marcel L'Abbe) that the interference in conduction is due to secondary inflammatory or degenerative processes engrafted on the margins of the septal defects, the resultant fibrous tissue causing pressure on the bundle or its branches, or the inflammatory process destroying them.

The auriculoventricular conduction system is normal in cases with defects of the subaortic septum and persistent total truncus. The extremely rare congenital anomalies of the conduction system per se are displacement of the sinus node, abnormal course of the auriculoventricular conduction system or abnormal neighboring relations (Monckeberg). Morrison's case showed a blind ending of the left branch and hypertrophy of the right branch of the bundle of His. In Sato's case there was transposition of both branches of the conduction system with normal position of auricles and transposition of the venous ostia.

Laubry cited a case seen with Mougeot in a man 60 years of age, with bradycardia and complete dissociation of conduction between auricle and ventricle in whom a latent defect of the interventricular septum was found at postmortem examination. This lesion was interpreted as a point of departure of inflammatory lesions that caused destruction of the bundle.

The regularity and the large diphasic form of the ventricular complexes, and the slightly prolonged conduction time over a period of observation of two and one-half years in the presence of auricular fibrillation, suggest that the ventricles in my second case are activated by an idioventricular center. In form, the ventricular complexes suggest a bundle branch block of the common type. The present controversy as to the types of bundle branch lesions (Wilson and his co-workers), the presence of dextrocardia and the lack of positive evidence as to the relation of the chambers of the heart due to the unusual electrocardiogram, make it hazardous to interpret the location of the idioventricular rhythm and the question of ventricular predominance.

In a case of complete situs inversus, Potts and Ashman encountered similar considerations with the exception that they were definitely dealing with a mirror-picture heart. The electrocardiogram showed "right ventricular predominance, ventricular ectopic beats and retrograde conduction." The diagnosis of partial left (functional right) bundle branch block was entertained but not favored because of the observations of Wilson and Hermann that the QRS complex varies with the cardiac rate in the presence of partial bundle branch block and auricular fibrillation, and the right ventricular predominance attributed in the absence of any cardiac hypertrophy to the rotation of the heart around its longitudinal axis.

In Meyer's case, studied by the roentgenogram and the electrocardiogram, complete heart block was accompanied by complete cardiovascular transposition, pulmonary stenosis and defect of the interventricular septum. In lead I of this case, P and T were inverted, R only slightly, S was highly upright (left ventricular predominance) and leads II and III replaced each other. This case, that of Abbott and Moffatt, and my cases show beyond doubt the expression in the electrocardiogram of the combined influence of axis deviation and direction of electrical potential of situs inversus, right ventricular hypertrophy and conduction defects associated with congenital cardiac disease or malformation.

My second case and that of Krestin are the only cases of isolated dextrocardia associated with auricular fibrillation. The latter case is attributed to an acquired mitral stenosis. In my case the auricular fibrillation cannot be explained on the basis of a congenital lesion but possibly as the result of a long-standing (congenital) heart block.

In the absence of confirmatory evidence in the electrocardiogram, my diagnosis of dextrocardia with normally related ventricles rests entirely on the interpretation of the roentgenogram. In my opinion, it is the right ventricle that is hypertrophied and in the presence of situs inversus of the ventricles would not give the cardiac contour observed here.

HISTORY OF THE SUBJECT

Severinus of Rome (1643) first noted dextrocardia in complete situs inversus. Soon after, the first anatomic case of a dextrocardia occurring in a partial heterotaxia was recognized by Moellenbrock and Hoffmann. Senac, in 1749, divided cases of dextrocardia into acquired and congenital types. Eschenbach (1769) described a case of isolated dextrocardia with transposition of the aorta, including its abdominal portion, recorded in Ferrein's Anatomy (1741) (vide Aufermauer citing Gruber, Krieger). Geoffrey St Hilaire (1832) collected 60 cases of dextrocardia, 30 of which were not accompanied by transposition of other organs (cf Falck). Boillaud (1835) (cf Krieger) first recognized isolated dextrocardia clinically and differentiated between displacement and transposition of the heart. DeBeauvais³⁷ pointed out the importance of differentiating the isolated form from complete situs inversus. Mosler (1866), Schroetter (1870) and Pope (1882) gave early clinical descriptions. The first roentgenographic observation of an isolated dextrocardia was made by Vehsemeyer. Stoerk (1911) made the first electrocardiographic study of a case of dextrocardia (Rosler), but the first detailed electrocardiographic record was made by Moffett and Neuhof (1915) in an isolated dextrocardia with inversion of the chambers. Weinberger believed his 2 cases to be the first isolated cases with inversion of the chambers to be studied by electrocardiograms. Anderson described anatomically isolated dextrocardia occurring in a mouse.

GENERAL CONSIDERATIONS

ETIOLOGY

The familial incidence of dextrocardia in complete situs inversus has been noted in twins (Reinhardt), two brothers (Lowenthal, Ochsenius, Reid, Carpenter), three brothers (Carpenter), brother and sister (Curschmann, Neuhof), two children in one family, sex not given (Frohlich) and in four generations (Lancisi). Familial incidence has also been noted by Rogi, Leroux, Labbe and Barret, Baumann, Liotta and Bianchi. In isolated dextrocardia, the familial incidence has been denied by Clerc and Bobrie and Mandelstamm and Reinberg. The only instances I find are that of Doolittle, in father and son in a family with two generations of twins, and that of Boruttau and Stadelmann in a maternal uncle.

The incidence of twins in families with dextrocardia is confined to these cases of Doolittle, Reinhardt, MacLennan and Schott, Schmilinsky and Nagel referred to 2 cases in a series of 24 isolated dextrocardias. A family history of cardiac disease is reported by Bahn in his case and in 5 other instances (Baumgarth, Mosler, Sussmann, Neumann, Guss). Nagel also referred to 5 instances. Rosler noted this in his first case.

and emphasized consanguineous marriage in relation to congenital cardiac disease. Abrahamson noted a family history of rheumatic fever in a case of total situs inversus (case 3). In my series a family history of cardiac disease was found in 9 cases and of rheumatic fever in 3 cases. A history of acute articular rheumatism was given in 6 cases.

The age incidence studied by Clerc and Bobrie in 57 cases of isolated dextrocardia was found to be 6 persons under 1 year, 12 in the first decade of life, 12 in the second, 13 in the third, 2 in the fourth and 3 older than 50 years (63 years, Pope and Lucchi, 67, Giovannini). In Rosler's collection of 24 cases that came to necropsy, there were 11 in the first year of life, 4 in the first decade of life, 2 in the second, 1 in the third, 3 in the fourth, 2 in the fifth, none in the sixth and 1 in the seventh, the average age was 14 years. In his series of 127 clinical cases, the average age was $23\frac{1}{2}$ years with the following age incidence: first year of life, 5 cases, first decade, 26, second, 28, third, 28, fourth, 18, fifth, 5, sixth, 7, seventh, 1, and eighth, 1. In my entire series of 144 cases with age given, in the first year of life there were 17 cases, in the first decade, 31, in the second, 24, in the third, 30, in the fourth, 21, in the fifth, 12, in the sixth, 5, in the seventh, 3, and in the eighth, 1.

There were 42 males in Clerc and Bobrie's series of 56 cases. In Nagel's collection of 24 cases, 16 occurred in males and 4 in females, in 3 cases the sex was not given. In Rosler's collection of 24 anatomic cases, 10 were in males, 10 in females and in 4 cases the sex was not given. In my series, in those cases in which sex is mentioned 89 were in males and 51 in females. In the cases verified by necropsy, the ratio of sexes is 1:1, in the clinical series it is approximately 2:1, which is the ratio given by Kuchenmeister for cases of complete situs inversus. Baumann attributed this apparent predominance in males to the fact that many of the reported cases were found in army recruits, and that the breasts of women make the detection of dextrocardia improbable on casual examination.

Congenital skeletal deformities associated with accepted cases of dextrocardia have been reported by Tison (thirteen ribs on the right side, eleven on the left, sixth and seventh fused), by Henoch, in a case of isolated dextrocardia (absence of radius and left thumb), by Wagner (total hemiatrophy of the right side of the face), by Mandelstamm and Reinberg (case 7b, isolated dextrocardia with fissure of sternum, and a case of complete situs inversus in a boy of 17 with a supernumerary sixth finger and accessory cervical mammae), by Grunfeld (congenital umbilical hernia), by Moffett and Neuhof (metacarpal deformities), by Rosler (case 3, finger defects, syndactylism of toes, cervical rib, fissure of sternum) and by Sakurai in a case of partial heterotaxia (harelip and cleft palate).

Intra-uterine traumatism or disease as a factor in the causation of dextroposition has been emphasized by Berwald, Pic and Alaux, and also by Cade, Rebattu and Gras in whose case an early pleurisy, which later disappeared, presumably caused the right-sided heart. In Berwald's case, incorrectly reported as a genuine case of pure congenital dextrocardia, the left pectoral muscle was absent and the left ribs depressed at the sternum. At necropsy, the pericardium was found adherent to the wall of the chest, and the apex pointed to the left. The anomaly in this case must be attributed to intra-uterine traumatism. (For a series of similar cases of "Rechtslage" of the heart associated with defects of the rib, muscle and sternum see "Cases of Congenital Dextroversion" under "Special Lists of Cases," second installment.) Uterine fibroids may press on the growing fetus and cause such deformities. Transitory traumatism may alter the position of the heart without leaving a trace of deformity of the thorax owing to the elasticity of the growing thoracic wall.

In cases of complete situs inversus, left-handedness has been noted in from 48 to 50 per cent (Scandola) and in 23 of 31 cases (Ebstein). In LeWald's series of 28 cases of complete situs inversus and 1 of isolated dextrocardia, all of the patients were right-handed. Weygandt considered left-handedness as evidence of a partial situs inversus with transposition of the cerebral hemispheres. Among the cases of isolated dextrocardia, right-handedness is the rule, but left-handedness has been noted by Sobierczyk and by Vehsemeyer, by Nagel in 3 of 5 cases and by Bonheim in his case, Mandelstamm and Reinberg noted no case in a series of 5 of 7 cases of isolated dextrocardia in which mention is made of dexterity and 3 with a history of left-handedness in a series of 26 cases of total situs inversus. In my series, left-handedness occurred in 5 of 15 cases in which this point was noted.

The lower position of the right testicle is a more dependable sign of heterotaxia than left-handedness. Ebstein observed the right testicle to be lower in 28 of 36 cases of complete situs inversus, Mandelstamm and Reinberg, in 6 of 9 men with total situs inversus, and Royer and Wilson, in a case of incomplete heterotaxia. In my second case, the testicles were in normal position.

The frequency of cases of isolated dextrocardia reported by different authors vary according to their definition and their discrimination of suitable cases.

Breschet, 1826. Ill defined group of anatomic cases mainly of the acquired type, 1 case of isolated dextrocardia.

Schroetter, 1870. Ill defined.

Krieger, 1880. 16 cases, presumably isolated but not well defined.

Vehsemeyer, 1897. 27 cases.

Aufdermauer, 1907. 55 cases.

- Nagel, 1909 23 cases from the German literature, 16, clinical only
 Herxheimer, 1910 40 cases, 17 with necropsy
 Foggie, 1910 46 cases, clinical only, 7, necropsy only, 5, clinical and necropsy, with a sixth personal case
 Moffett and Neuhof, 1915 124 cases, but obviously not all isolated as claimed
 Clerc and Bobrie, 1918 50 cases, clinical only, 11, post mortem, 23 of 55, complicated (collection too large, in spite of care claimed in selection)
 Laubry and Pezzi, 1921 60 cases including 1 personal case, 29 with necropsy
 Mandelstamm and Reinberg, 1928 7 additional personal cases
 Rosler, 1930 24 cases with necropsy, 127 cases of "Rechtslage" of the heart, some cases of congenital dextroversion included, 7 personal cases added to literature
 Lichtman 1931 10 cases, necropsy only, 26 cases, clinical and necropsy, 125 cases, clinical only, 2 personal cases added

GENESIS OF ISOLATED DEXTROCARDIA

A review of the literature indicates that little progress has been made in the knowledge of the real cause of this anomaly. The numerous theories advanced to explain the cause of total situs inversus may be briefly alluded to: turning of the embryo itself (Baer, Remak, Bischoff, B. S. Schultze), primary turning of the cardiac tube (Dajeste), twisting of the umbilical cord to the left in the fetus (Vuchow), persistence of the right omphalomesenteric and umbilical veins instead of the left (Lochte) and the twin theory of Schott and Foister, (reviewed by Nagel, Paltauf, Reinberg, Fulchiero, Aufdermauer, Mandelstamm and Reinberg, Laubry and Pezzi and others).

The mechanism of the isolated type of dextrocardia must necessarily be even less understood, especially since many variations are involved. Rindfleisch explained partial heterotaxia as due to the physical mechanism of the altered flow of the blood column. Marchand showed long ago that the reasons for the development and existence of total and partial situs inversus differ from each other markedly, and that these conditions owe their origin to different factors.

However, it may be stated with some certainty that chronologically the dextrocardia of total situs inversus occurs in the earliest phase of the development of the embryo not later than the tenth to the fifteenth day after fertilization of the ovum, when the S-shaped curve of the primary embryonal heart tube takes place (Herxheimer, Monckeberg), at this time, a contrasigmoid turning of the cardiac tube occurs instead of the usual sigmoid twist.

By a careful and systematic investigation of the anatomic material in cases of partial heterotaxia, such as Pernkopf has made, interesting data pertaining to the concept of the genesis of the different types of dextrocardia have been obtained. The contention of Lochte that transposition of isolated organs in one body cavity cannot occur in associa-

tion with a normal relationship in the other is disproved. Pernkopf demonstrated that different organs or organ complexes or parts thereof may develop a mirror-image position, and that the anlage of an organ in the sense of its normal or inverse symmetry exerts no influence on the development of the form or position of an adjacent organ. It is his opinion that the different components of the embryonic heart may develop in an independent manner and unrelated to one another in the sense of a situs inversus. A situs solitus of a single organ has been observed in spite of a general situs inversus. Cases of complete situs inversus with sinistocardia must be considered as instances (Hickman and others).

The time of incidence of the isolated inversions of the entire cardiac organ complex or individual parts must also occur as early in embryonic development as they do in complete situs inversus. According to Spitzer, total situs inversus and partial situs inversus are fundamentally identical in genesis (Marchand and Lochte believe they differ, the latter occurring later in embryologic development). According to him, they represent the contrary to the normal phylogenetically developed organ. The isolated inversions correspond to inversion of the primary genetic divisions of the anlage of the heart, the sinus, the primary atrial, the primary ventricular or bulbus metameres or the entire cardiac metameric complex. The malformation usually associated with isolated cardiac inversion must necessarily occur because anatomic and functional continuity is maintained despite the fact that correlated portions of the heart do not undergo simultaneous inversion. The rules governing the transposition of the bulbus metamere differ from the rest of the cardiac complex.

It is Spitzer's concept that transposition of the vessels is a result of a combination of recent and atavistic phylogenetic and ontogenetic influences on the development of the bulbus metamere. In his opinion, in the evolution of the lung-breathing terrestrial species from the aquatic gill-breathing types, the pulmonary portion of the cardiac tubes assumed a rôle as important as the systemic portion with a consequent development of both these systems side by side separated by septums. In order, however, that aerated blood may reach the systemic circulation, a complete torsion through an angle of 180 degrees of the arterial end must take place, so that aerated pulmonary blood may go to the left side of the heart and be discharged therefrom, and nonaerated systemic blood may go to the right side of the heart and be discharged into the lungs. That such a rotation occurs is seen in the clockwise spiral of the aortopulmonary septum. Thus in the definitive heart, as the pulmonary trunk descends it swings from behind the aorta around to the left and anteriorly, reversing proximally its distal relationship to the

aortic trunk When the vascular growth of the fetus is impaired, the development of the pulmonic side of the heart and the septum is usually interfered with, and so-called "detorsion defects" occur There is a complete absence of the 180 degrees spiral rotation of the arterial end or only to a variable degree, resulting in the different types of transposition of the great vessels This underlying detorsion at the arterial end of the cardiac tube does not entail any countertorsion at the venous end of the heart A group of cases of dextrocardia without inversion of the chambers with anomalies of the great vessels may be considered as mechanically the result of detorsion defects (cf Paltauf, Lochte, Shapiro's case 1) A group of cases of dextrocardia with inversion of the ventricles with so-called "corrected transposition" of the great vessels (Lochte, Paltauf) and so-called dextroversion with transposition of the great vessels may be explained as the opposite in genesis teleologically of the two anomalies, the transposition of the vessels and the inversion of the chambers (Rosler and Spitzer's case) The dextrocardia associated with persistent right aortic arch may similarly be explained on a mechanical basis

The second type of isolated dextrocardia without inversion of the chambers is considered by Nagel to be due to an arrest of development occurring in the teratogenetic-termination period of about the sixth week At this time the normal heart fully developed occupies a median position in the thorax almost symmetrically perpendicular to the long axis of the body, with slight preponderance of the right ventricle At this point the heart fails to rotate to the left as normally and rotates with its apex to the right with a slight degree of torsion of the vascular pedicle *

The preponderance of the right ventricle is probably an important but not the sole factor in the pathogenesis of this type Truly most of these cases have right-sided congenital malformations but so do cases of congenital cardiac disease without dextrocardia Furthermore, there are cases of dextrocardia of this type without malformations (Pope, Lucchi, Wendling) The higher blood pressure and the normal overgrowth of the left ventricle may account for the normal deflection of the heart to the left Paltauf believed the upward growth of the predominant right lobe of the liver or a transient fetal hydropneumothorax

* A group of borderline cases designated as "mesocardias" belongs here I must insist for acceptance under the heading of true dextrocardia that the apex lie to the right Gorter erroneously implies that in isolated dextrocardia the apex lies to the left Cases of median heart erroneously reported as dextrocardia follow anatomically verified, Sandifort, Wilson, Otto, Breschet, Kussmaul, Pernkopf's case 4, clinical only, Schroetter, Stone, Hochsinger (roentgenogram), Gorter (roentgenogram)

to be responsible for the normal turning of the heart to the left Broman, concurring, expressed the belief that the right lobe of the liver growing cranialward meets the heart in descent, diverting it to the left. An abnormally large left lobe of the liver has been considered the cause of the turning of the apex of the heart to the right (Shapiro's case 1).

The occurrence of three uncomplicated cases of dextrocardia without inversion of the chambers nullifies the contention of Paltauf and of Kundrat that a normal heart cannot occur in dextrocardia because it would result in kinking of the great vessels. Clerc and Bobrie maintained that these uncomplicated cases prove the later intra-uterine development of this type since a normal heart and blood vessels have already been formed. They also disprove the theory that the associated malformations are the result of the dextrocardia (Nagel believed that pulmonary stenosis was the result of the dextrocardia). Pic and Alaux contended that this type of dextrocardia appeared late in fetal life and was the result of associated anomalies, and that uncomplicated cases could not be congenital. Fetal endocarditis (Pal), pleuropericardial adhesions (Cipriani, Steiner, Kuchenmeister, Walther) and intra-uterine traumatism (Aperte, Laubry and Pezzi) have been incriminated as causing the simple type of dextrocardia.

In summary, it may be said that the dextrocardia with inversion is teratogenetic in origin, occurring in the first two weeks of embryonic life and the associated malformations being secondary to the anatomically deranged portions of the cardiac complex. Dextrocardia with normal relationship of the chambers is a result of certain unknown mechanical factors or transposition of the great vessels, in which case the anomaly occurs in the sixth week, or later, of embryologic development. The malformations associated with this type of dextrocardia may be necessary factors in the cause of the anomaly or the result of the same underlying etiologic factor.

ANATOMY

In anatomic consideration of a case of isolated dextrocardia, two factors are of primary importance, first, that the transposition of the heart is not part of a general heterotaxia, and second, its inner architecture.

The so-called "ideal" mirror-image dextrocardia is attained only as part of a total situs inversus. The statement of Laubry and Pezzi that even in total situs inversus complete mirror-image dextrocardia does not exist, the great vessels not sharing in the mirror-image of the normal, the aorta lying anteriorly and on the right and the pulmonary artery lying posteriorly and on the left, rests on a confusion with the

isolated mirror-picture type of dextrocardia. Except for the position of the great vessels, the isolated mirror-picture dextrocardia may at least theoretically be virtually identical with that of total situs inversus. The axis of the heart then runs from above on the left downward to the right and anteriorly with the apex comprised of the right arterial ventricle pointing to the right (in complicated cases the apex is formed by the right ventricle transposed to the left). The right arterial ventricle contains a bicuspid valve and gives rise to the aorta which contrary to its normal left and posterior position passes to the right and forward and after deviation to the left curves on itself back to the right side and crosses the right bronchus (right aortic arch) or as frequently the left bronchus (Rosler) but only rarely descends along the right side of the vertebral column. Most commonly, after crossing the right or left bronchi, it descends along the left of the vertebral column. The anterior aspect of the heart is formed by the left venous ventricle which lies under the sternum, possesses a tricuspid valve that discharges blood into the pulmonary artery, and therefore represents the normal right ventricle. The superior and inferior venae cavae run on the left of the vertebral column and empty into the left venous auricle.

To date, however, an "ideal" mirror-image isolated dextrocardia has never been observed anatomically (Bard, Pic and Alaux, Stone, Paltauf, Nagel, Mandelstamm and Reinberg, Lauby and Pezzi). Rosler further maintained that no case exists at present with complete inversion of all the chambers of the heart. In addition to the aforementioned nonparticipation of the vessels in the mirror-image dextrocardia, cardiovascular lesions or inversions of individual segments of the cardiac complex occur. Among Rosler's 24 cases with anatomic study, there was no case with situs inversus and normal origin of vessels and there were in the literature 7 cases with abnormal origin of the blood vessels (Breschet, Reddingius, Lochte, Baumgaith, Wenner, Ratner, Abbott, Beattie, Rosler, Spitzer). Of this group an equal number of cases showed defective, or absent, septums. In at least half the cases there were changes in the pulmonary orifice. The aortic arch was found on the right as often as on the left. There was isolated inversion of the ventricular region four times (Lochte, Wenner, Ratner, Abbott, Rosler, Spitzer), of the pulmonary or caval veins, partial, twice (Breschet, Ratner, Abbott) and complete, twice (Reddingius, Baumgaith). The nearest approach to the realization of a mirror-image isolated dextrocardia is found in Graanboom's case, in which, however, a tricuspid valve was found in the right arterial ventricle, a mitral valve in the left, venous, side of the heart and the origin of the aorta on the right side and anterior to the pulmonary artery.

CASES OF ISOLATED DEXTROCARDIA STUDIED ANATOMICALLY ONLY

1 Eschenbach,¹⁰¹ 1769 Male, aged 6 years, apex of heart to right, base toward left (small portion to left of midline), great vessels inverted in respect to thoracic cavity, abdominal aorta to right of vertebral column, other organs in normal position (The original article appeared in Latin, little else is recorded)

2 Otto,²⁴⁸ 1824 New-born child, median heart with apex pointing to right, rotation to left on long axis so that right border is anterior and left side of heart not seen, right auricle anterior, left auricle posterior, right ventricle short, one half the normal length, left ventricle of normal length forming entire apex of heart, great vessels normal, descending aorta on left side, small round septal defect, lungs normal, left smaller but has no cardiac incisure

3 Breschet,⁵⁷ 1826 Dissection by Meckel at Foundling Hospital of Paris Fibrous pericarditis, apex of heart to right, bilocular heart, persistent left superior vena cava in addition to normal right superior and inferior venae cavae, single large arterial trunk from ventricle crossing to right side of vertebral column, vestige of tricuspid valve, single ventricle communicates with auricles and aorta by two orifices, aortic valve normal, pulmonary artery does not enter ventricle, situated to the left and behind the aorta, liver, stomach, portal vein and intestinal tract normal, spleen absent, spina bifida, large thymus, lungs, three lobes each

4 Pope,²⁶⁴ 1882 Anterior flap of mitral valve adherent to endocardium with some thickening, arch of aorta in central thorax, descending aorta to left of vertebral column, branches in normal relationship, heart otherwise normal, gray hepatization of lungs, right, three lobes, larger than left, left, two lobes, abdominal organs in normal position

5 and 6 Boerhaave⁵⁰ Two doubtful cases, incomplete data

Case 1, male executed prisoner, all viscera in normal position except heart, the apex of which pointed to the right

Case 2, female executed prisoner, the so-called right chamber of the heart on the left and the left vice versa

7 Northrup,²⁴⁵ 1888 Female infant, 31 days old, cyanosis, heart inclined to right side, bilocular heart, single artery, the aorta, rudimentary septal ridge, pulmonary artery, a fibrous cord, superior vena cava on left of aorta, aorta on left of vertebral column, absence of pulmonary veins, absent mitral orifice, aortic orifice valve and tricuspid auriculoventricular valve, anomalous abdominal veins, left lobe of lung, two lobes, abdominal organs in normal position by inference of text

8 Kundrat,¹⁸⁹ 1888 Female, 4 weeks old, cyanotic at birth, trilocular heart (two auricles), aorta anteriorly from giant venous ventricle, pulmonary artery posteriorly from small arterial ventricle, liver normal in size and position but left lobe greater than right, gallbladder more to the left than usual, stomach normal, spleen absent, duodenum double sling, anomalous course of portal vein

9 Reddingius,²⁷³ 1889 and Graanboom,¹⁷⁶ 1881 Icterus, ascites, pulmonary infarction, hemothorax (right), left serofibrinous pleurisy, apex of heart formed by both ventricles, aorta, normal course and branches, superior vena cava on left, pulmonary artery posterior to aorta, right ventricle anterior, left, posterior, aortic lumen narrow, tricuspid valve in right arterial ventricle, mitral valve in left venous ventricle, inversion of ventricles with corrected transposed vessels, not mirror-image heart, left lung, two lobes

10 Holt,¹⁶³ 1890 Death from pleuropneumonia, trilocular heart biatriatum, septal ridge gives rudimentary left ventricle and major right ventricle (three fourths of heart), tricuspid, mitral and pulmonary orifices normal in right ventricle, aorta from common cavity, stenosis of orifice of pulmonary artery, aorta and branches normal, right auricle in normal position, larger than left, foramen ovale patent chambers in normal position, cardiac incisure at left middle lobe

11 Grunmach,¹⁴⁶ 1890 Death from tuberculosis, pleuritis, adherent to pericardium but not responsible for displacement, right ventricle forms round apex, larger than left (which does not reach apex), right ventricle and auricle hypertrophied and dilated, contains tricuspid valve, persistent foramen ovale, pulmonary conus stenosis, absent pulmonary valve, ventricular septum defect, aorta from left ventricle, right aortic arch behind esophagus (note error in illustration), no transposition of vessels or chambers

12 Birmingham,⁴⁸ 1892 Pulmonary tuberculosis, especially of left lung, apex of heart formed by tip of right ventricle, anterior surface formed by both ventricles equally, aorta and pulmonary artery from right ventricle, persistent right aortic arch ventricular and auricular septal defects, persistent left superior vena cava, no auricular appendage to right of aorta, pulmonary artery posterior and to the right of the aorta, stenosed, anomalous valve, ventricular cavities normal, mitral valve in left ventricle, transposed aorta, abdominal organs normal

13 Lochte,²⁰⁷ 1894 Male, aged 46, died of cardiac failure, atherosclerosis, chronic myocarditis, apex formed by right ventricle, anterior surface of heart formed by small right ventricle and large left ventricle, aorta to left and anterior, pulmonary artery posterior, bicuspid valve in right ventricle, giving rise to pulmonary artery, tricuspid valve in left ventricle giving rise to aorta, minute ventricle septal defect, auricles and ventricles not transposed, auriculoventricular valves transposed, corrected transposition of vessels, lungs not transposed

14 Dalton,⁹⁰ 1898 Short clinical note Male, aged 15 years, splenomegalia, liver on right side, death due to embolism, abdominal organs not mentioned at necropsy, right lung, two lobes, pulmonary artery more exposed than usual, persistent left superior vena cava, mitral endocarditis, apex of heart beneath right sixth rib, $2\frac{1}{2}$ inches from midsternum

15 Lowenthal,²⁰⁸ 1900 Apex formed by right ventricle, left ventricle very small right ventricle larger and thicker walled, ventricular septal defect, pulmonary artery absent, ductus botalli takes place of pulmonary artery, forms arterial trunk, superior vena cava on right, ventricles in normal relationship, abdominal organs normal

16 Baumgarth,³¹ 1902 Left lung, four lobes, single auricle receives two superior venae cavae, four pulmonary veins, and inferior vena cava, externally auricles appear reversed, primitive interventricular communication, right ventricle wide and strong, aorta from left ventricle, rudimentary stump of pulmonary artery in corrected transposition, patent ductus botalli, branches of aorta in normal relationship, cor biloculare with normal relationship of chambers, corrected transposition of vessels

17 Lucchi,²¹⁰ 1902 No anomaly of great vessels or auricles, dilatation of aortic arch, calcification of aortic valve, dilatation of left and right ventricles, no incisure of left lung, chronic passive congestion of normally situated abdominal organs

18 Wendling,³⁵¹ 1903 Dilated aorta, liver enlarged, normal position of abdominal organs, heart enlarged, valves normal, normal relationship of cham-

bers, apparently a normal heart, obvious postmortem rotation of apex to left, lobes of lung normal, pulmonary tuberculosis

19 Wright and Drake,³⁶⁶ 1903 Single large aorta-like vessel (bilocular heart) from superior and anterior parts of ventricle, curves like aorta, rudimentary auricular and ventricular septums, single valve between auricle and ventricle, more like bicuspid than tricuspid, normal position of abdominal organs

20 Wenner,³⁵² 1909 Case 9, female, aged 10½ years, cor monoventriculare biatriatum, transposition of arterial vessels, aorta anterior, pulmonary artery stenosed, posterior, both originating from right half of heart, apex points to right in right midaxillary line at level of eighth rib, mitral valve on right, tricuspid valve on left, persistent left superior vena cava as well as normal right, no arterial outlet to left chamber, three semilunar cusps in aorta, only two in pulmonary artery, anomalous position of atria, right huge, left small, aorta gives off branches as usual and follows usual course to left of vertebral column, abdominal organs not mentioned specifically but text infers normal position

21 Pal,²⁵¹ and Gruss,¹⁴⁷ 1888, 1907, 1919 Female, aged 49 years, died of meningitis, deformity of chest, right lung adherent, three lobes, heart free, left chambers enlarged, right auricle more posterior than usual, aorta from left ventricle which is thicker than right, pulmonary artery from right ventricle, mitral valve normal, aortic valve calcareous, stenosed, great vessels normal, chambers in normal relationship, aortic stenosis, due to fetal endocarditis, abdominal organs normal

22 Nagel,²³⁹ 1909 Apex formed by right posterior, poorly developed ventricle, auricular septal defect, absent septum membranaceum, pulmonary artery from right ventricle, aorta from left ventricle which has bicuspid valve, pulmonary conus and ostium absent, aorta arises on left, anterior to pulmonary artery, runs to right behind esophagus, descends on left of vertebral column, inferior and superior venae cavae on right of vertebral column, three lobes in both lungs

23 Foggie,¹¹⁴ 1910 Heart enlarged, only right auricular appendage present, mitral and tricuspid valves incompetent, right ventricle forms greater part of anterior aspect of heart, cor triloculare biventriculare, liver in normal position

24 Campergue,⁶⁶ 1912 Died with vomiting and dyspnea, congestion of lungs, liver and spleen normal, globular heart with apex deviated toward right border, dilated right auricle, tricuspid valve normal, hypertrophied right ventricle, left auricle receives vena cava, left ventricle gives off pulmonary artery (stenosed), aorta dilated, ventricular septal defect, transposition of vessels

25 Morgan,²³⁴ 1916 Female, aged 9 months, death following convulsions, lungs not inverted, liver, spleen and stomach normal, heart globular, left ventricle thick, right thin, valves normal, aortic arch exaggerated, branches in normal position, patent foramen ovale, no septal defect

26 Mautner and Lowy,²¹⁶ 1921 All organs except heart in normal position, hypertrophied globular heart, apex formed by right ventricle, normal arch over left bronchus, pulmonary artery covered by aorta, cor triloculare biatriatum, right ventricle larger than left, mitral valve normal in left auriculoventricular ostium, pulmonary artery stenosed, transposition of aorta

27 Ratner, Abbott and Beattie,²⁷² 1921 Female, aged 17 days, heart enlarged, apex broad, formed by both ventricles, globular in shape, right pleural transudate, auricles normal, transposition of ventricles and great vessels, right (systemic) ventricle smaller than left, tricuspid valve on left, mitral on right, ventricular septum entire, auricular septum absent (cor triloculare biventriculare), ascending

aorta from right ventricle to left, arch and descending on right, patent ductus arteriosus, aortic isthmus stenosis, right pulmonary veins into right part of common auricle, superior vena cava into persistent omphalomesenteric bay

28 Plumier-Clermont,²⁶⁰ 1924 Very small right ventricle, septal defect, riding aorta crossing right bronchus, one auricle receiving right and left venae cavae and pulmonary veins, stenosis of pulmonary artery, auriculoventricular valves normal, death from pulmonary tuberculosis

29 Reggiani,²⁷⁴ 1925 Female, aged 2½ months, cor triloculare biatriatum, apex formed by both ventricles, auricular septal defects, left side of heart with four-leaved auriculoventricular valve, aorta and pulmonary artery from right side of heart, aorta anterior to pulmonary artery, both course to right upward, patent ductus arteriosus, two coronaries with single ostium, abnormal cardiac veins

30 Pol²⁶¹ and Bahn,²⁵ 1925 Male, aged 40 years, atresia of aorta beyond origin of subclavian artery, normal situs of vessels, cardiac incisure in right three-lobed lung, hypertrophied left ventricle, aortic endocarditis (lenta), recurrent mitral endocarditis, aortic isthmus stenosis, calcified tuberculosis of both apices

31 MacCallum and Resnik,²¹¹ 1926 Cor triloculare biatriatum, patent foramen ovale, large ventricular septal defect, narrow, anterior aorta crosses left bronchus, pulmonary artery posterior and wide, mitral valve on left, tricuspid on right side, vena cavae and pulmonary veins in their normal auricles, ductus arteriosus closed

32 Biedermann,⁴⁶ 1926 Female, aged 36 years, septal defect, pulmonary insufficiency, and stenosis, two-leaved pulmonary valve, aorta anterior and left from left ventricle, pulmonary artery posterior and right from right ventricle (corrected transposition), tricuspid valve on right side, mitral on left, aorta runs on left

33 Garvin,¹²⁷ 1927 Short case presentation, no clinical notes, age and sex not given, one auricle, one ventricle, two pulmonary arteries arise symmetrically from the thoracic aorta, pulmonary veins empty into superior vena cava, inferior vena cava absent, congenitally absent spleen

34 Rach,²⁷¹ 1927 Male, aged 4 months, apex formed by right ventricle, apex points to right, marked eccentric hypertrophy of right ventricle and right auricle with patent ductus arteriosus and foramen ovale, tracheal stenosis due to compression of right lung by hypertrophied heart

35 Rosler²⁸⁸ and Spitzer,³²⁰ 1929 Male, aged 6 years, abdominal organs normal, pulmonary artery and aorta (left side) arise side by side, parallel from anterior border of junction of both ventricles, aorta crosses right bronchus, branches in reverse order, right ventricle has mitral valve, pulmonary conus atresia, smaller left ventricle has tricuspid valve, aorta and three-leaved normal valve, septal defect, ductus botalli and foramen ovale open, auricles and caval veins in normal relationship, transposition of aorta, pulmonary conus atresia, isolated inversion of ventricles and truncal regions, right-sided aortic arch

36 Shapiro,²⁰⁷ 1930 Male, aged 14 months, pulmonary tuberculosis with cavitation, ulcerative ileitis, miliary tuberculosis of both lungs, spleen absent, left lobe of liver larger, common auricle leading to incompletely divided ventricular cavity which empties by single arterial trunk, pulmonary artery absent, rudimentary ventricular septum, right ventricle insignificantly small, left large, forms apex, large bicuspid auriculoventricular leaflet, single larger arterial vessel with three semilunar cusps, detorsion defect of truncus arteriosus with reversal of coronary arteries

CLASSIFICATION

A practical classification by Mandelstamm and Reinberg of cases of dextrocardia in its broader sense into four main types (type I, as found in total situs inversus, type II, isolated dextrocardia with mirror-image arrangement of chambers, type III, isolated dextrocardia with normal relationship of chambers, type IV, acquired dextrocardia) is criticized by Rosler as not being fully applicable to cases as verified anatomically. Rosler has enlarged on this classification from the point of view of his definition of "Rechtslage" of the heart, including cases of congenital dextroversion consistent with anatomic findings of proved cases.

The classification I propose for dextrocardia in its strict sense is simple, practical and faithful to the anatomic variations observed, or possible.

- I According to degree of heterotaxia
 - A Nonisolated, occurring as part of a complete situs inversus
 - B Isolated, heart alone transposed
 - C Partial heterotaxia-dextrocardia associated with transposition of some other organ or portions of the vascular system
- II According to the arrangement of the chambers and great vessels
 - A With normal arrangement of the chambers
 - 1 Arch of aorta crossing left bronchus
 - 2 Arch of aorta crossing right bronchus
 - 3 Persistent right aortic arch
 - 4 Transposition of the great vessels
 - 5 "Corrected transposition" of the great vessels
 - B With mirror-picture arrangement of chambers
 - 1-5 As under A
- III According to the presence or absence of complications
 - A Uncomplicated, not associated with congenital malformation or disease
 - B Complicated
 - 1 Atresia or stenosis of pulmonary and aortic orifices or pulmonary conus
 - 2 Septal defects, auricular and ventricular
 - 3 Anomalies of number of chambers of heart, cor biloculare and triloculare
 - 4 Venous anomalies
 - 5 Anomaly of valve ostia, position, number and cusps
 - 6 Patent foramen ovale and ductus botalli

In all instances the apex of the heart lies to the right, and the axis is directed from the left above downward to the right. The mediastinum is in the midline, except for slight deviation of the trachea, esophagus and great veins. The ventricle constituting the apex of the heart is too variable anatomically to permit clinical classification. Since most

cases encountered thus far do not belong to any single clearcut group, in classifying any particular case it is necessary to designate the various key numbers and subgroups of the classification for a complete description of the case. For the clinical application of such a scheme in cases not verified by necropsy, roentgenographic and electrocardiographic observations are essential.

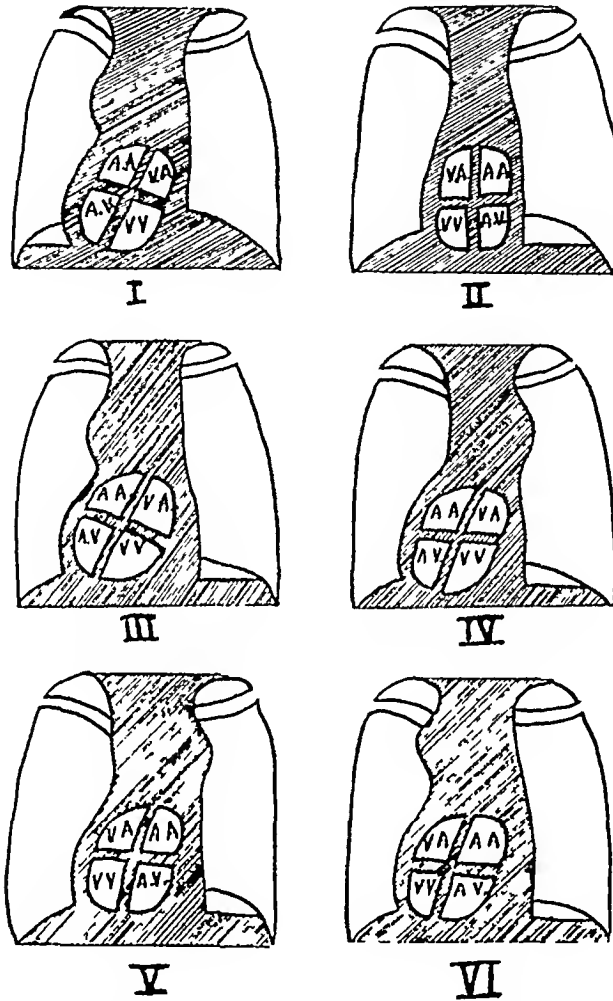


Fig. 7—Composite schematic representation of the anatomic and roentgenographic types and variations of isolated congenital dextrocardia, *I*, mirror-image dextrocardia as found in complete situs inversus, stomach transposed also, *II*, mesocardia with apex to right side, *III*, mirror-image isolated dextrocardia with right aortic arch, *IV*, mirror-image isolated dextrocardia with left aortic arch, *V*, isolated dextrocardia with normally related chambers and left aortic arch, *VI*, isolated dextrocardia with normally related chambers and right aortic arch. The right aortic arch crosses the right bronchus and may descend on the left or right of the vertebral column. With a persistent right aortic arch, the aorta crosses behind the esophagus to descend on the left of the vertebral column.

In figure 7, the types and variations of isolated dextrocardia are represented schematically.

CLINICAL OBSERVATIONS BASED ON CASES REPORTED IN THE
LITERATURE

Cases of isolated dextrocardia complicated by gross malformations are recognized at birth or early in life by the classic signs of congenital cardiac disease. Uncomplicated cases or cases with minor malformations, on the other hand, are only casually discovered by the patient by an exaggerated pulsation in the right side of the chest, by a subjective sensation of a surging feeling or palpitation in the right side of the chest, by the clinician in the course of a routine physical examination in civilian or military life or by the pathologist at necropsy.

The analysis of the cases reported in the literature, including the two personal cases, is based on a study of

- I 10 cases studied by necropsy only
- II 26 cases studied by necropsy and also clinically
- III 125 cases studied clinically only

These cases are here enumerated in their respective groups, chronologically with a record of year, age, sex and roentgenogram and electrocardiogram if taken.

I Cases studied by necropsy only

(1) Eschenbach,¹⁰¹ 1769, male, 6 years, (2) Otto,²⁴⁸ 1824, new-born child, (3) Breschet,⁵⁷ 1826, (4 and 5) Boerhaave,⁵⁰ male and female adults, (6) Northrup,²⁴⁵ 1888, female, 31 days, (7) Kundrat,¹⁸⁰ 1888, female, 4 weeks, (8) Dalton,⁹⁰ 1898, male, 15 years, (9) Wenner,³⁵² 1909, female, 10½ years, (10) Garvin,¹²⁷ 1927, age and sex?

II Cases studied by necropsy and also clinically

(1) Pope,²⁶⁴ 1882, male, 41 years, (2) Reddingius,²⁷³ and Graanboom,¹³⁶ 1889, 1891, male, 33 years, (3) Holt,¹⁶³ 1890, male, 15 months, (4) Grunmach,¹⁴⁶ 1890, male, 15 years, (5) Birmingham,⁴⁸ 1892, female, 20 years, (6) Lochte,²⁰⁷ 1894, male, 46 years, (7) Lowenthal,²⁰⁸ 1900, female, 10 months, (8) Baumgarth,³⁴ 1902, sex ?, 11 months, (9) Lucchi,²¹⁰ 1902, male, 63 years, (10) Wendling,³⁵¹ 1903, male, 43 years, (11) Wright and Drake,³⁶⁶ 1903, male, 10 months, (12) Pal,²⁵¹ and Gruss,¹⁴⁷ 1909, 1888, female, 49 years, roentgenogram, (13) Nagel,²³⁹ 1909, female, 1 month, roentgenogram, (14) Foggie,¹¹⁴ 1910, male, 2 10/12 years, roentgenogram, (15) Campergue,⁶⁶ 1912, male, 8 years, (16) Morgan,²³⁴ 1916, female, 9 months, roentgenogram, (17) Mautner and Lowy,²¹⁶ 1921, male, 5 years, roentgenogram, (18) Ratner, Abbott and Beattie,²⁷² 1921, female, 17 days, (19) Plumier-Clermont,²⁶⁰ 1924, sex ?, 14 months, electrocardiogram, (20) Reggiani,²⁷⁴ 1925, female, 2½ months, (21) Pol,²⁶¹ and Bahn,²⁵ 1925, male, 40 years, roentgenogram, electrocardiogram, (22) MacCallum and Resnik,²¹¹ 1926, sex ?, 10 weeks, electrocardiogram, (23) Biedermann,⁴⁶ 1926, female, 36 years, roentgenogram, electrocardiogram, (24) Rach,²⁷¹ 1927, male, 4 months, roentgenogram, electrocardiogram, (25) Rosler,²⁸⁸ and Spitzer,³²⁰ 1929, 1930, male, 6 years, roentgenogram, electrocardiogram, (26) Shapiro,²⁹⁷ 1930, male, 14 months.

III Cases studied clinically only

(1) Jasinski,¹⁶⁷ 1861, male, 25 years, (2) Mosler,²³⁶ 1866, male, 20 years, (3) Schroetter,³⁰⁵ 1870, male, 32 years, (4) Bienfait,⁴⁷ 1873, age and sex ?, (5)

Accolas,⁵ 1875, male, 52 years, (6) Ziemssen,³⁶⁹ 1876, male, 28 years, (7) Mosler,²³⁶ Falck,¹⁰³ 1877, female, 36 years, (8) Leichtenstern,¹⁹⁷ Wehn,³¹⁷ his case 2, 1880, male, 19 years, (9) Henoch,¹⁵⁴ 1880, female, 11 years, (10) Bramwell,⁵⁵ 1881, male, 39 years, (11) Theocare,³³² 1881, male, 54 years, (12) Wehn,³⁴⁷ case 1, 1882, male, 27 years, (13) Mayerhofer,²¹⁷ 1883, male, 30 years, (14) Van Zant,³⁶⁸ 1884, male, 31 years, (15) Sussmann,³³⁰ 1887, male, 15 years, (16) Schroetter,³⁰⁵ 1887, male, 22 years, (17) Anselmi,¹⁶ 1888, male, 20 years, (18) Michel,²²⁴ 1888, male, 22 years, (19) Grunfeld,¹⁴⁵ 1889, female, 44 years, (20) Wilks and Moxon,³⁵⁹ 1889, female, 3 years, (21) Adie,⁷ 1890, female, 25 years, (22) Arnaud,¹⁷ 1891, male, 32 years, (23) Becker,³⁸ 1891, male, 25 years, (24) Schott,³⁰⁴ 1891, male, 46 years, (25) Hawkins,¹⁵⁰ 1891, male, 12 years, (26) Bard,²⁹ 1892, female, 16 years, (27) Carmichael,⁷¹ 1893, male, 7 years, (28) Storen,³²⁸ 1894, male, age ?, (29) Schroetter,³⁰⁵ 1894, male, 21 years, (30) Gingeot-Bard,³⁰ Petit and Ravaut,²⁵⁹ 1895, 1897, 1898, male, 30 years, (31) Sobierajczyk,³¹⁹ Vehsemeyer,³¹² 1896, 1897, male, 15 years, roentgenogram, (32) MacLennan,²¹² 1869, male, 15 years, (33) Gerrard,¹³² 1896, female, 26 years, (34) Berks,⁴² 1896, male, 3½ years, (35) Bramwell,⁵⁶ 1896, female, 5 years, (36) Middleton,²²⁵ 1898, male, 38 years, (37) Senator,³¹⁰ 1899, male, 6 years, roentgenogram, (38) Leo,¹⁹⁹ 1899, male, 8 years, roentgenogram, (39) Angyan,¹⁵ 1899, female, 21 years, roentgenogram, (40) Bonheim,⁵¹ 1900, male, 7 years, roentgenogram, (41) Crispino,⁸⁵ 1900, female, 55 years, roentgenogram, (42), Schmilinsky,³⁰² 1900, female, 9 years, roentgenogram, (43) Chapman,⁷⁷ 1900, male, 40 years, (44) Frommer,¹²¹ 1900, female, 52 years, (45) Monks,²³³ 1901, male, 28 years, (46) Gossage,¹³⁵ 1901, female, 46 years, (47) Ziemssen and Rieder,³⁷⁰ 1902, male, 16 years, roentgenogram, (48) Darnall,⁹¹ 1902, female, 69 years, (49) Wagner,³⁴⁵ 1902, male, 23 years, roentgenogram, (50) Flatau,¹¹¹ 1903, female, 37 years, (51) Parkinson,²⁵⁴ 1903, male, 6 years, (52) Benfey,³⁹ 1903, male, 6 years, (53) McIver,²¹⁹ 1905, male, 32 years, (54) Quadrone,²⁷⁰ 1905, male, 25 years, roentgenogram, (55) Hochsinger,¹⁵⁸ 1906, sex? 7 months, roentgenogram, (56) Sheffield,³¹⁴ 1906, female, 8 years, roentgenogram, (57) Neumann,²⁴¹ 1906, male, 20 years, roentgenogram, (58) Aufdermauer,²¹ case 1, 1907, male, 50 years, (59) Aufdermauer, case 6, male, 30 years, (60) Aufdermauer, case 7, female, 76 years, roentgenogram, (61) Doolittle,⁹⁴ 1907, male, 41 years, (62) Tate,³³¹ 1907, male, adult, roentgenogram, (63) Hawthorne,¹⁵¹ 1907, male, 11 years, (64) Scandola,²⁹⁶ 1909, male, 40 years, (65) Carpenter,⁷² 1909, sex?, 5 years, (66) Cautley,⁷⁵ 1909, male, 7 years, (67) Whyte,³⁵⁷ 1910, female, between 5 and 10 years, (68) Stoerk,³²³ 1911, male, 11 years, electrocardiogram, (69) Geissler,¹³⁰ 1911, male, adult, (70) Vanderwelde,³¹⁰ Cantineau-Vandeput,³³⁸ 1911, 1912, male, 14 years, roentgenogram, (71) Brooks,⁶⁰ 1911, female, 13 years, (72) Culcer-Petresco,⁸⁶ 1912, female, 9 years, roentgenogram, (73) Giovannini,¹³³ 1913, female, 67 years, roentgenogram, (74) Tison,³³³ 1914, sex?, 4 years, roentgenogram, (75) Botteri,⁵³ 1914, female, 36 years, roentgenogram, (76) Moffett and Neuhoof,²²⁹ 1915, male, 3½ years, electrocardiogram, (77) Martin,²¹⁴ 1915, male, 19 years, roentgenogram, (78) Stolkind,³²⁵ 1816, male, 52 years, roentgenogram, (79) Aitken,¹⁰ 1917, male, 17 years, roentgenogram, (80) Clerc and Bobrie,⁸⁰ 1917, male, 29 years, roentgenogram, (81) Boruttau and Stadelmann,⁵² 1917, age and sex?, roentgenogram, electrocardiogram, (82) Indemnas,¹⁶⁶ 1918, male, 25 years, roentgenogram, (83) Duval,⁹⁷ 1919, male, adult, roentgenogram, (84) Parsons-Smith,²⁵⁵ case 3, 1919, male, 31 years, (85) Parsons-Smith, case 4, male, 27 years, (86) Hesselgren,¹⁵⁶ 1919, sex?, 14 days, roentgenogram, (87) Weinberger,³⁴⁹ case 1, 1919, male, 47 years, roentgenogram, electrocardiogram, (88) Weinberger, case 2, female, 21 years, roentgenogram, electrocardiogram, (89)

Vaquez and Donzelot,⁴¹¹ case 2, 1920, male, 21 years roentgenogram, electrocardiogram, (90) Reinberg, same as case 5 of Mandelstamm and Reinberg,²¹³ 1922, male, 35 years, roentgenogram, electrocardiogram, (91) Fumaioli,¹²⁴ 1922, female, 18 months, (92) Meyer,²²³ 1923, female, 17½ years, roentgenogram, electrocardiogram, (93) Curschmann,⁸⁸ 1924, male, 40 years, electrocardiogram, (94) Jones,¹⁶⁹ case 3, 1924, female, 35 years, roentgenogram, electrocardiogram, (95) Jones, case 4, male, 27 years, roentgenogram, electrocardiogram, (96) Fulchiero and Bruno,¹²³ 1924, male, 22 years, roentgenogram, electrocardiogram, (94) Augey,²² 1924-1925, age?, sex?, (98) Gorter,¹³⁴ case 1, 1925, sex?, 4 months, roentgenogram, electrocardiogram, (99) Gorter, case 2, sex?, 2 years, electrocardiogram, (100) Gorter, case 4, female, 7 years, roentgenogram, electrocardiogram, (101) Gorter, case 5, sex?, 4 months, (102) Capon and Chamberlain,⁶⁹ 1925, female, 26 months, roentgenogram, electrocardiogram, (103) LeWald,²⁰² 1925, female, 24 years, roentgenogram, electrocardiogram, (104) Ponzio,²⁶³ 1926, sex?, age?, roentgenogram, (105) Gautier and Coeytaux,¹²⁸ 1926, male, 18 months, roentgenogram, electrocardiogram, (106) Lenk,¹⁹⁸ 1926, female, 14 years, roentgenogram, electrocardiogram, (107) Colvin,⁸² 1926, female, 28 years, roentgenogram, electrocardiogram, (108) Prendergrass,⁶⁹ 1927, sex?, age?, roentgenogram, (109) Aime,⁹ 1927, sex?, age?, roentgenogram, (110) Krestin,¹⁸⁴ 1927, female, 30 years, roentgenogram, electrocardiogram, (111) Milani,²²⁶ 1928, female, 27 years, roentgenogram, (112) Loben,²⁰⁶ 1928, male, 22 years, roentgenogram, (113) Mandelstamm and Reinberg,²¹³ case 6, 1928, male, 36 years, roentgenogram, electrocardiogram, (114) Mandelstamm and Reinberg, case 7 sex and age?, roentgenogram, (115) Mandelstamm and Reinberg, case 7a, female, 7 years, roentgenogram, electrocardiogram, (116) Mandelstamm and Reinberg, case 7b, sex?, 15 years, roentgenogram, electrocardiogram, (117) Mandelstamm and Reinberg, case 9, female, 14 years, roentgenogram, electrocardiogram, (118) Strothmann,³²⁹ 1929, male, 9 years, roentgenogram, electrocardiogram, (119) Rosler,²⁸⁸ case 1 (see Rosler and Spitzer's case with necropsy), case 2, 1930, male, 17 years, roentgenogram, electrocardiogram, (120) Rosler, case 3, female, 11 years, roentgenogram, electrocardiogram, (121) Rosler, case 4, male, 33 years, roentgenogram, electrocardiogram, (122) Rosler, case 5, female, 36 years, roentgenogram, electrocardiogram, (123) Rosler, case 7, male, 27 years, roentgenogram, (124) Lichtman, case 1, 1931, female, 21 years, roentgenogram, electrocardiogram, (125) Lichtman, case 2, male, 46 years, roentgenogram, electrocardiogram

Analysis of the cases collected from the literature, totaling 161 (including 2 personal cases), indicates that the majority occur in males (87 and 51) and that there is a greater incidence in the first three decades of life. In the entire series only 3 cases proved clinically and anatomically to be uncomplicated by a congenital cardiac malformation (Pope, Lucchi, Wendling), while 45 (of 150 cases) were frankly complicated with clinical symptoms and signs of congenital cardiac disease. Rosler denied the existence of an uncomplicated case. The nature of the malformations in these cases is listed as follows:

Pulmonary stenosis and septal defect

Clinical (7 cases) Wehn, case 2, Hawkins, Fumaioli, Strothmann, Wardrop, Griffith?, Bonheim?, Lenk?

Necropsy (4 cases) Baumgarth, pulmonary artery absent, Campergue, Mautner and Lowy, Biedermann

- Pulmonary stenosis, ventricular septal defect, patent foramen ovale or auricular septum defect
 Necropsy (5 cases) Holt, Grunmach, Birmingham, Nagel, pulmonary artery absent, Plumier-Clermont
- Pulmonary stenosis, ventricular septal defect and patent ductus arteriosus
 Clinical (2 cases) Berks, Moffett and Neuhof, with patent foramen ovale
 Necropsy (1 case) Rosler, Spitzer, with patent foramen ovale
- Disease of pulmonary artery alone
 Clinical (4 cases) Mayershofer², Adie, Gorter, cases 1² and 4
- Auricular septal defect or patent foramen ovale and ventricular septal defect
 Clinical (1 case) Lichtman, case 2²
 Necropsy (3 cases) MacCallum and Resnik, Wright and Drake, Shapiro, pulmonary artery absent
- Septal defect alone
 Clinical (8 cases) Bramwell², Middleton², Hochsinger, Culcer-Petresco
 Parsons-Smith, case 4, Fulchiero and Bruno, Milan, Lichtman, case 1
 Necropsy (1 case) Lochte
- Patent ductus arteriosus, with auricular and ventricular septal defects
 Necropsy (1 case) Reggiani
- Patent ductus arteriosus auricular septal defect, aortic stenosis
 Necropsy (1 case) Ratner, Abbott and Beattie
- Patent ductus arteriosus and foramen ovale
 Clinical (1 case) Weinberger, case 2
- Aortic stenosis
 Clinical (1 case) Curschmann
 Necropsy (2 cases) Pal, Gruss, Pol, Bahn
- Patent foramen ovale or auricular septal defect alone
 Necropsy (1 case) Foggie

In seven cases of the series there was a history of acute articular rheumatism (Grunfeld, Genaid, Gossage, Parkinson, McIver, Weinberger, case 1, Rosler, case 4), in fourteen, acquired valvular disease (Theocard, Bard, Angyan [?], Quadione [?], Hawthorne, Geissler, case 5, Jones, case 4, Kiestin, Pope, Graanboom, Lucchi, Pol, Bahn, Aufdermauer, case 7, Weinberger, case 1), in four, signs of cardiac hypertrophy alone (Vehsemeyer, Mosler, Bienfait, Arnaud), and in eight, only symptoms of cardiac trouble (Accolas, Schott, Gungeot, Bard, Petit and Ravaut, Dainall, Stoerk, Giovannini, Meyer, Jones, case 3). Forty-two cases showed definitely normal heart sounds and 6 cases that came to necropsy had shown normal sounds (Lowenthal, Baumgarth, Wendling, Wright and Drake, Rosler, Spitzer, Shapiro). A history or evidence of extracardiac intrathoracic disease (pleurisy, pneumonia, pulmonary tuberculosis, pericarditis) was present in 32 cases and thoracic asymmetry or deformity of scoliosis of the dorsal spine in 23 cases.

In 10 cases in which the relative position of the testicles was noted only in 1 case was the right lower (Scandola). In 15 cases in which

TABLE 1—Cases of Isolated Congenital Dextrocardia Studied Clinically, by Roentgenogram, Electrocardiogram and by Necropsy

Roentgenogram										Electrocardiogram										Necropsy				
Aorta					Diaphragm					P					QRS						T			
Author and Date	Sex and Age	Family History, or Cardiac Twins	Right or Left Handed	Ties	Cardiac Symptoms	Abnormal Cardiac Signs	Arch	Descending	Abdominal Organs	Cardiac Shadow	Left Lung	Right ?	?	I	II	III	I	II	III	I	II	III	T	Comment
1 Plummer and Clermont, ²⁰⁰ 1924	?	0	0	0	Cyanosis, clubbing, polyemia, cardiac malformation, Fallot type	Systolic murmur at base	Right bronchus (post mortem only)	?		Right		?												No illu trations or other data
2 Polak and Bahn, ²¹¹ 1925	Male 40 yrs	Mother died of heart disease	0	0	Dyspnea, 4 weeks, slight cyanosis and clubbing	Systolic murmur over valvular areas	Left (first oblique view)	Left	Stomach normal (CO ₂ gas), spleen and liver normal	Right	?													Atresia of aorta beyond origin of subclavian, normal situs of ves sels, cardiac measure in right three lobed lung, hypertrophy of left ventricle, aortic endocarditis (lenta), recurrent mitral endo carditis, aortic isthmus stenosis, calcified tuberculous of both apexes
3 Bieder mann, ⁴⁰ 1926	Male 36 yrs								Right	Both equi level														Septal defect, pulmonary insuffi ciency and stenosis, two leafed pulmonary valve, aorta anterior and left from left ventricle, pul monary artery posterior, and right from right ventricle, cor rected transposition, transposed on right, mitral on left, aorta runs on left of vertebral column
4 Rosler ²²⁵ and Spitz er, ³²⁶ 1929 1930	Male 6 yrs	Younger brother has congenital heart disease, consanguineous marriage	0	0	Morbus coeruleus, no murmurs at birth, syncope and spasms first year, cyanosis, clubbing fingers and toes, polyemia	Heart sounds pure, no thrill, liver, three finger breadths below right costal margin	Right bronchus	Right of vertebral column	Stomach normal	Right trans versely slight degree, left ven tricle forms apex														Abdominal organs normal, pul monary artery and aorta (left) arise side by side, parallel from anterior border of junction of both ventricles, aorta crosses right bronchus, branches of aorta in re verse order, right ventricle has mitral valve, pulmonary conus atresia, smaller left ventricle has transposed valve, aorta and three leafed normal valve, septal de fects, ductus botalli and foramen ovale open, auricles and caval veins in normal relation, trans position of aorta, pulmonary conus atresia, isolated inversion of ventricle and truncal regions, right sided aortic arch

dexterity was considered, left-handedness occurred in 5 (Parsons-Smith, case 4, Doolittle, Bonheim, Sobierczyk, Vehsemeyer, Mosler, Falck)

Inversion of the chambers of the heart was claimed in 19 cases of the series

Physical signs only (3 cases) Mosler, Sussmann, Schroetter

Roentgenograms (2 cases) Schmilinsky, Weinberger, case 1?

Electrocardiogram (10 cases) Moffett and Neuhoof, Meyer, LeWald, Gorter, case 5, Capon and Chamberlain, Moffett and Neuhoof, case 9, Strothmann, Rosler, Spitzer, Rosler, case 5, Lichtman, case 1

Necropsy (4 cases) Graanboom, Breschet, Ferrein, Eschenbach, Rosler, Spitzer

It is of interest to note that the 3 uncomplicated cases in the series (proved by necropsy) belong to the type of dextrocardia with normally related chambers

Significant roentgenographic and electrocardiographic features and points of diagnostic significance will be discussed under their respective headings

In table 1 are tabulated the findings in the only 4 cases in the literature which were studied clinically, by roentgenogram, electrocardiogram and by necropsy

(To be concluded)

Book Reviews

THE DEVELOPMENT OF PHYSIOLOGICAL CHEMISTRY IN THE UNITED STATES
By RUSSELL H CHITTENDEN American Chemical Society, Monograph
Series Price, \$6 Pp 427 New York The Chemical Catalog Company,
Inc, 1930

This monograph constitutes an excellent review of the major part of the graduate instruction and more important investigative work in physiologic chemistry in most of the educational and research institutes in the United States. The historical treatment in the first part of the book clearly shows the influence of European training on the earlier physiologic chemists of the United States as well as the later and rapid growth of a new school, largely through the development of separate departments of physiologic chemistry or biochemistry in the larger institutions. The author later emphasizes that the subject of physiologic chemistry should be recognized and "treated as a pure science unhampered in its growth by any form of application," that it "should have perfect freedom to progress and expand in any and all directions without regard to possible applications" and that "applications will come fast enough as the science advances." Many phases of biologic chemistry are reviewed very fairly and relatively completely, while other contributions of equal importance or prominence or equally recent and of equally long standing are rather conspicuously absent. It was, to be sure, impossible to include all American contributions to physiologic chemistry in so limited a volume, but it may be questioned whether the space now devoted to enumerating academic records of men, similar to the information given in "American Men of Science," had not been utilized more profitably and fairly for the addition of obvious omissions. The Yale influence is, of course, obvious in many instances, partly because of its real influence and secondly because of the author's years of association and interest.

AFFECTIONS DOULOUREUSES DE L'INTESTIN TERMINAL By C BONORINO
UDAUNDO and L V SANGUINETTI Price, 9 francs Pp 24 Paris
Gaston Doin, 1931

The chief value of this publication is that it calls attention to the so-called functional pains in the recto-anal regions. The author contends that pain associated with conditions in the lowest colonic segments is sufficiently characteristic so that one is usually able to suspect the cause.

The anatomy of the rectum and anus is described, following which functional pains are discussed in some detail. Such pains are either lancinating or severe burning with griping, occur most frequently at night, last from ten minutes to an hour, are influenced very little by defecation, and appear in attacks with intervals of freedom. They are really neuralgias. Illustrative cases are cited. It is pointed out that functional pains may be present with some organic lesions, for example, hemorrhoids, and that surgical treatment for such a painful condition usually fails to give relief. No one satisfactory treatment is known.

Pains due to organic lesions are discussed, but this adds little to the general knowledge of these conditions.

THE INTERNATIONAL MEDICAL ANNUAL FOR 1931 Edited by CAREY F COOMBS and A RENDLE SHORT Price, \$6 Pp 551 New York William Wood & Company

This is the forty-ninth year book, written by English and Canadian authors. The editors' purpose is to furnish a digest of the world's medical literature, critically considered and reduced to a small bulk by competent authorities. As a rule, pathology is not included in the discussions, but particular attention is called to new and improved methods of diagnosis and treatment that seem promising. Each article is signed, so that the reader may know the identity of the author. The subjects are arranged alphabetically, and ample references are given.

The Annual has an interesting introduction by the editors which outlines many of the new and important advances in medicine during the year. These are covered in greater detail in the book. A section on diseases of the teeth is included in this edition. The articles are well written, and the authors have confined themselves to matters of importance. As must be expected in such a book, minor details cannot be included, but the original articles are always referred to.

The book is valuable to any one doing general work who does not have much time for extensive reading. All branches of medicine are covered, and a wealth of material is condensed in a readable manner.

LA FOLIE ET LA GUERRE DE 1914-1918 By A RODIET and A FRIBOURG-BLANC Price, 30 francs Pp 194 Paris Felix Alcan, 1930

This book represents a study of about 2,500 observations of mental disturbances arising among French troops during the World War, in an attempt to answer the following questions: 1. Are there war psychoses constituting special mental diseases differing in origin and evolution from the ordinary psychoses in times of peace? 2. Does war favor the development of the usual psychoses observed in times of peace and increase their number?

The first question is answered in the negative. The second question is answered in the affirmative, and arguments are presented to prove that the increase in number of the usual psychoses is due to exciting causes such as emotional shocks, physical misery, wounds, contusions, infections and intoxications (especially alcohol) which are augmented by the conditions of war.

GRUNDZUGE DER NEUROCHIRURGIE By WALTER LEHMANN Price, 13 50 marks Pp 197 Leipzig Theodor Steinkopff, 1930

In this small volume are considered in brief the operative procedures that have to do with most of the neurosurgical conditions of the central nervous system. It is obvious that in so few pages very little detail has been attained. Nevertheless, for a general surgeon the conceptions of the neurosurgeon are well expressed. That holds especially for traumatic lesions of the brain, fracture of the skull and intracranial hemorrhage. As far as the tumors themselves go, the subject matter is totally inadequate.

The author discusses surgery of the peripheral nerves of the vegetative nervous system, of painful diseases and of spastic paralysis, so that a general survey of the neurosurgical methods can be obtained from a perusal of this work. The book is highly recommended for the general surgeon. The specialist, however, will not gain much from it.

CANCER By WILLY MEYER Price, \$7 50 Pp 427 New York Paul B Hoeber, Inc, 1931

This volume of 427 pages includes both an experimental and a clinical study of the etiology and treatment of carcinoma. There is an enormous collection of evidence of various sorts indicating the presence of alkalosis as the most important

etiologic factor, and the author's treatment is based on trying to reverse the metabolic status in the production of an acidosis

While the reviewer would not subscribe to the acceptance of the interpretation placed on the evidence by Dr Meyer, either clinically or experimentally, he feels that the book is worth while simply as a compilation of data and a statement of the present standing of a very controversial subject

LES REACTIONS VASO-MOTRICES DU FOIE, EN CLINIQUE By DR ROGER
GLENARD, Paris Paper Price, 30 francs Pp 240, with 19 illustrations
Paris Gaston Doin, 1931

This is another monograph of the usual type on the diagnosis and therapy of disorders of the liver, not so much disorders of hepatic function, as disorders of the size and position of the liver Methods of palpitation, roentgen outlining, etc, are described in detail, and figures are presented It is a useful manual for the physician familiar with the French language, but contains nothing particularly new

CORRECTION

In the article by Dr Eli Moschcowitz entitled, "The Relation of Achlorhydria to Pernicious Anemia," in the August issue (ARCH INT MED 48 171, 1931), 0 21 per cent at the end of the fourth line from the bottom on page 172 and at the beginning of the sixth line from the top of page 173, referring to the incidence of achlorhydria, should read 2 1

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THE INFLUENCE OF SOLAR RAYS ON METABOLISM

.

WITH SPECIAL REFERENCE TO SULPHUR AND TO PELLAGRA
IN SOUTHERN UNITED STATES

JAMES H SMITH, M D
RICHMOND, VA

THE INFLUENCE OF SOLAR RAYS ON METABOLISM

WITH SPECIAL REFERENCE TO SULPHUR AND TO PELLAGRA
IN SOUTHERN UNITED STATES ¹

JAMES H SMITH, M D

RICHMOND, VA

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INTRODUCTION

That there are biologic effects due to radiant energy is not open to question, and that some of these are related to pellagra seems probable

* Submitted for publication, Dec 15, 1930

¹ From the Medical Department, McGuire Clinic and St Luke's Hospital

In epidemic or endemic disease, the experimental laboratory studies so necessary for scientific proof can rarely be undertaken before a fairly complete survey of outstanding epidemiologic features has been made. With regard to pellagra, it is believed that climatic factors, while often referred to, have not received the consideration required for an understanding of the disease. The significance of established factors in the etiology of any disease is not depreciated and may be enhanced by recognition of other significant factors. It is easy to imagine such a result in connection with pellagra when the etiology of rickets is considered, with its interrelated influence of calcium and phosphorus imbalance and deficiency in vitamin D and in ultraviolet rays. In this connection there is recognizable a significance in the condition of the patient in relation to lack of exposure to ultraviolet rays similar to the relation between the resistance of the patient and the virulence of the infection. One factor may be present in a degree of intensity less than the average for the development of the disease, and the disease may still develop because of a greater than average intensity of another factor. The same considerations possibly are applicable to pellagra.

Certain observations bearing on the influence of solar rays in metabolism and in pellagra will be presented, but the only support brought from experimental investigations is taken from the work of others. The data are far from complete and are not always in agreement. The available literature has been reviewed only in part. In general, the study is intended as a basis for further experimental work and as a basis for contemporary observation as suggested by analysis of past events. However, under controlled experimentation and observation with a limited number of subjects, there would remain the possibility that the sampling or selection of subjects failed to take into account some undetermined factor of individual metabolism present in some but not in others of the general population and conditioning the end-result. Such an explanation may account for the fact that a condition considered to be pellagra developed in only six of Goldberger and Wheeler's experimental subjects.

The more significant climatic factors are temperature, humidity, movement of air (wind) and sunlight. Various studies have been undertaken to determine their exact influence on both plant and animal life, including that of man. For example, Tsi-Tung Li¹⁰² calculated partial correlation coefficients for the influence of these factors on the suction force of sap in certain plants, and he gave a coefficient of 163 for the temperature of air, 445 for the intensity of light and 469 for the relative humidity. In the human subject, when the relative humidity is 100 per cent, the minimum metabolism occurs when the temperature of

the air is from 75 to 80 F⁴⁴ These factors will be referred to again, and the effect of ultraviolet irradiation on metabolism will be considered in detail

On reaching the earth's surface, solar radiation is affected by several factors, including latitude and season With regard to seasonal variations in biologic phenomena, many instances are matters of common knowledge and many others are well established through special investigation and observation Rarely is it possible to assign distinct and independent significance to a single climatic factor, and what influence any factor has may be mediated through any one or more of several factors, such as vegetation, the intake of vegetables and mineral and animal food, bacterial or parasitic invasion, or the transmission of disease through an intermediate host, such as the mosquito

North of the equator (and all references are to the northern hemisphere unless otherwise stated), the summer and winter seasons present the opposite phenomena of maturing and decaying vegetation In summer, the intake of protein is decreased, and in the winter it is increased In summer, the iodine content of water and salt is decreased, and the resistance of white mice to nitrile is decreased In the latitudes from which these data are reported, the iodine content of the thyroid gland is lowest in March, and about the same season the development of goiter is highest Following the winter months, rickets also reaches its highest seasonal incidence, along with its observed disturbance of calcium-phosphorus metabolism The list could be extended The seasonal variations of pellagra will be reserved for further discussion

As introductory and suggestive of certain of the ideas to be developed, attention is directed to certain studies of *Paramecia* and of the lens of the eye

Paramecia were subjected to ultraviolet rays that had previously passed through solutions of cystine $\left\{ \left\{ \text{CH}_2\text{S}-\text{CH} \begin{array}{l} \nearrow \text{NH}_2 \\ \searrow \text{COOH} \end{array} \right\} \right\}_2$ in sodium hydroxide⁴⁰ The time of exposure required to produce fatal results was 1,200 seconds, if the ultraviolet rays first passed through the cystine solution, as compared with 150 seconds in the controls From this it is argued that susceptibility of protoplasm to ultraviolet radiation is conditioned by the selective absorption of the toxic rays by cystine—and certain aromatic amino-acids Ward,¹¹⁴ in his studies of the absorption spectra of amino-acids, found that cystine was the only amino-acid that had any marked absorption in the region of solar ultraviolet rays It would appear that the relatively high concentration of cystine in wool and hair is of physiologic importance in the protection of the organism against the harmful effects of prolonged exposure to sunlight⁵⁹ The eyelashes

may be endowed with a function more delicate than that of protecting the eye against the entrance of foreign bodies

Light of wave length 760 to 380 $m\mu$ (the lower limit being variable and depending to some extent on the age of the individual) penetrates to the retina and is perceived as visible light. Light from 380 to 295 $m\mu$ is absorbed by the lens and causes it to fluoresce. Light of wave length shorter than 295 $m\mu$ is absorbed by the cornea and conjunctiva, producing a severe ophthalmia.¹⁵

Although it is possible that heat may be a contributing cause in glass-blowers' cataract, there is no evidence of injury to the eye by heat except in eclipse blindness, which is probably due to heat coagulation of the retina.

Light from 295 to 385 $m\mu$ although absorbed by the lens, produces no ill effect as a rule. Most proteins are coagulated by the ultraviolet light which they absorb, but the lens protein seems to be resistant in this respect, at any rate for the wave lengths 295 to 385 $m\mu$. The light absorbed by the lens causes a strong fluorescence in it, and Burge¹¹ suggests that the fluorescence constitutes a protective reaction, but the nature of the protection is not clear. It may be mentioned, as a matter of interest, that in some nocturnal animals (rats, mice) the lens does not fluoresce to waves of this length. Burge has shown by a series of ingenious experiments that, in the presence of certain salts, lens proteins coagulate with light longer than 300 $m\mu$, and he supposes that a combination of nutritive disturbances and strong light may account for the development of cataract. With this possible exception, however, the light absorbed by the lens is harmless.

Laurens stated⁵⁷ that there are two rather divergent and apparently conflicting ideas as to the influence of radiant energy as a causative element in the production of cataract. Both of them may be found to be compatible, for either the infra-red or the ultraviolet radiation may superinduce cataract under certain physiologic conditions of which nothing is as yet known (Sheard).

Gradle³⁴ has recently presented statistics as to the age of patients in various parts of the northern hemisphere operated on for senile cataract.

Table 1 gives the statistics and shows the geographic location of the surgeon as given by Gradle. A notation of the latitudinal location is also included. There is a noticeable tendency for the patient with cataract to be operated on earlier in the regions nearer the equator. Wright, in order to furnish a comparison of an equal number of Indian cases with the 4,230 Caucasian cases, carried his study far enough to serve this purpose, and he found that the Indian percentages remained practically what they were when worked on the first 500 tabulated. At Memphis, the next most southerly clinic quoted, the patients were not so young as the Indian patients, but were somewhat younger than the Caucasian group as a whole, as represented by the American and European cities farther north and including Memphis. In discussing the comparison between the Caucasian and the Indian people, Elschnig, of Prague, con-

sidered that it furnished good proof for the words that Hirschberg wrote in 1898 in the "History of Ophthalmology" "Under the glowing sun of India, cataract ripens fully twenty years earlier than with us"

Among the tissues of the body which give a strongly positive nitroprusside reaction, is the lens of the eye⁵⁹ Goldschmidt³³ has studied the cysteine content of the lens of cattle at various ages, as determined by the ability of the tissue to form hydrogen sulphide from elementary sulphur according to the general reaction

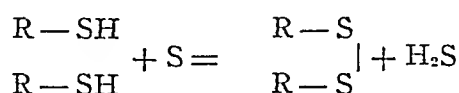


TABLE 1—*Age of Patients Operated on for Senile Cataract and Geographical Location of the Surgeon, as Reported by Gradle*

			Degrees Minutes	
1	Benedict	Rochester	43	30
2	Derby	Boston	42	30
3	Ellett	Memphis	35	
4	Elsehnig	Prague	50	
5	Kalt	Paris	49	
6	Knapp	New York	41	
7	Meller	Vienna	48	
8	Sinclair	Edinburgh	56	
9	van der Hoeve	Leiden	52	
10	Wessely	Munich	48	
11	Wright	Madras	12	
12	Gradle	Chicago	42	

Number	Latitude, Degree	Cases	20 30, per Cent	30 40, per Cent	40 50, per Cent	50 60, per Cent	60 70, per Cent	70 80, per Cent	80+, per Cent	
8	56	250	0 8	2 0	4 0	21 8	38 8	28 8	4 0	
9	52	100	0 0	0 0	2 0	16 0	39 0	31 0	12 0	
4	50	1,000	0 0	0 7	6 6	21 1	41 8	27 2	2 6	
5	49	500	1 0	1 6	6 8	18 8	37 6	30 6	3 8	
7	48	500	0 0	0 0	3 0	20 2	40 4	33 2	3 2	
10	48	509	0 0	0 0	2 9	12 6	36 9	41 7	5 9	
1	43	571	0 7	4 0	6 8	21 9	35 0	25 2	6 4	
2	42	100	0 0	0 0	6 0	20 0	45 0	28 0	1 0	
12	42	100	0 0	0 0	7 0	16 0	39 0	26 0	12 0	
6	41	100	0 0	1 0	1 0	24 0	41 0	27 0	6 0	
3	35	500	0 6	3 8	9 1	22 0	32 4	27 2	4 6	
11	12	500	0 2	4 4	15 8	29 6	41 2	8 4	0 4	
Average			4,730	0 21	1 40	5 86	20 28	38 95	27 74	5 56
Caucasian average			4,230	0 23	1 21	5 04	19 51	38 83	29 58	5 60
Indian average			500	0 2	4 4	15 8	29 6	41 2	8 4	0 4

The cysteine content of the lens, as determined by this method, varied little in calves between the ages of 8 days and 1 year, but there was a diminution of the cysteine content of the lens in adult life (1 3386 per cent cysteine in the lens of calves, 0 5820 per cent in the lens of cattle 8 to 17 years of age) No differences could be observed in the total sulphur content of the lens at different ages

In cataract of the lens, however, the nitroprusside reaction was absent and the lens was unable to reduce elementary sulphur to hydrogen sulphide If the lens was first treated with sodium sulphite (which reduces cystine to cysteine) the cataract tissue behaves as a normal lens, thus demonstrating that the failure of hydrogen sulphide formation was due, not to a cystine deficiency, but to the inability to form cysteine

Goldschmidt considers that the amount of cysteine present may determine the oxidative processes of the lens and play an important rôle in the pathology of cataract

THE EFFECTS OF SOLAR AND ULTRAVIOLET RAYS ON METABOLISM

In examination of the data with reference to the effects of solar and ultraviolet rays on metabolism discrepancies are noted, due doubtless at times to lack of standards of measurement of the rays and of influences by which they are modified, and to differences in the human and other animal subjects. The usual caution in applying to man the results of animal experimentation is necessary. In particular, with regard to vitamin B, birds and mammals appear to have different requirements, and it is further important to keep in mind a distinction between normal subjects on normal diets and abnormal subjects on abnormal diets. Attention will be directed more especially to the facts of protein metabolism as represented by nitrogen and sulphur, and to the basal metabolism.

Weiner (quoted by Laurens⁵⁷) carried out two long experiments on normal men, giving them irradiations from a carbon arc that did not have an ultraviolet ray shorter than 290 mμ, being comparable, therefore, to solar rays. During irradiation, the excretion of nitrogen was diminished, while after it there was a shift to a nitrogen equilibrium on a higher level than that present during the preliminary period and the negative balance became positive. Koenigsfeld, using a quartz mercury lamp, reported an opposite initial disturbance, but the same end-result of an increased retention of nitrogen. In Weiner's observations, the excretion of sulphur was not affected. Koenigsfeld found the elimination of sulphate increased. The emphasis here possibly belongs on the fact that in normal subjects the nitrogen equilibrium was reestablished on a higher level than before, and there was a retention of nitrogen.

Eichelberger's report is of especial interest in view of the observed low excretion of creatinine in pellagra. Eichelberger found that the excretion of creatinine is increased during an hour of irradiation (carbon arc or sunlight) and then decreased for several hours, after which it returns to the preliminary level. Possibly the emphasis here belongs on the secondary increase as the normal reaction. Heat was shown not to be a causative factor.

This is Hammett's conception of the conditions in sluggish ulcers of the skin (Hammett, reference 38). If further investigation should show that a similar disturbance of sulphur metabolism occurs in the tissues of the pellagrin, then by a slight stretch of the imagination, cataract could be looked on as pellagra of the lens, and the glass-blowers' cataract would represent the "dermal type," while the senile, and perhaps the diabetic, cataract would represent the "systemic type."

Laurens stated, "we might expect that transition from darkness to roomlight would produce results somewhat similar to irradiation with a strong source of radiant energy, but it is somewhat surprising to find that a change from light to darkness shows similar if less pronounced effects" The emphasis here seems clearly to belong on the influence of shifting conditions of ultraviolet exposure and introduces the principle of acclimation, the possible significance of which in pellagra appears largely to have been overlooked In a shift either way and following irradiation, there is a stimulation of endogenous nitrogen metabolism resulting in a decrease in the balance These experiments, as Laurens said, are indicative of a relationship between a positive or a negative variation in the amount of radiant energy acting on the organism and an initial disturbance of metabolism

Mayerson, Gunther and Laurens found that under the shifting influence of darkness to light, and vice versa, normal adult dogs on an adequate diet showed an initial effect of increased nitrogen metabolism, as shown by an increased excretion of urea and creatinine, which usually decreased to normal by the end of the period

From these and similar reports, the general conclusion seems to be warranted that moderate irradiation of normal subjects does not result in permanent change in the metabolism of proteins, and that for a time there is a shift to a nitrogen equilibrium on a higher level

THE INFLUENCE OF RADIANT ENERGY AND LATITUDE ON CARBOHYDRATE METABOLISM

The effect of radiant energy on carbohydrate metabolism has also received some attention from investigators Buige and Wickwie¹² found that *Paramecium caudatum* utilizes all of the simple sugars dextrose, levulose and galactose Dextrose and levulose are used more rapidly than galactose, as is the case with the higher animals

Ultraviolet radiation decreases the utilization of the sugars by these animal cells, without at the same time killing or injuring the cells

Ultraviolet radiation destroys insulin

The addition of insulin to the liquid containing the organisms prevents the decrease in sugar metabolism by the ultraviolet rays The decrease in the utilization of sugar brought about by ultraviolet radiation is attributed to the destruction of the insulin in the cells by irradiation

Cori and Cori¹⁷ reported that during the summer months, rats excrete an average of 62 mg of total acetone bodies per hundred grams of body weight per twenty-four hours, from the twenty-fourth to the forty-eighth hour of fasting During the winter months, the excretion of acetone bodies was only 19 mg The influence of temperature was excluded The ketosis was associated with a reduced capacity of the tissues to oxidize dextrose

Sundstroem⁹⁸ concluded that the level of the blood sugar in the tropics not only never reached an excessive height, but rather tends to occupy low levels. As a rule, descendants exhibit lower levels than immigrants. Mills⁹⁹ found that the death rate from diabetes increases as the distance from the equator becomes greater. Whether or not the observations of Sundstroem and of Mills will in any degree find a basis in those of Burge and Wickwire and of Cori and Cori is problematic. It appears rather that they tend to conflict. However, concerning the unicellular organisms studied by Burge and Wickwire, account should be taken of the possible influence in man of specialized tissue, such as the suprarenal glands, and the observations of Cori and Cori were in connection with rats during fasting rather than with the organism of man, on a diet normal for the environment.

THE PRESENT STATUS OF WATER-SOLUBLE VITAMIN B

A disturbance of nitrogen metabolism in pellagra, as evidenced by a study of the partition of nitrogen in the urine, has been described by several investigators, particularly by Sullivan and his co-workers. In contrast to the effects of ultraviolet irradiation under normal conditions is the statement of Eckstein (quoted by Laurens⁵⁷), that rats on a vitamin-free diet remain alive in comparatively good condition although their development is slow. If they are given irradiation, they die in from twelve to thirty-one days, "the disturbed metabolism not being able to stand the additional strain put upon it by radiation."

Extensive and prolonged experimental investigation has failed to yield an answer as to the chemical nature of the different factors involved in vitamin B, and the futility of attempting to deduce from observation the identity of the pellagra-preventive factor is too obvious to need comment. The complexity of the problem as it stands at present is clearly outlined in Kruse and McCollum's⁵⁴ recent review, from which the following abstracts were taken:

There is a difference of opinion regarding the effect of ultraviolet irradiation on the antineuritic principle. Working independently, Zilva and Spinka agreed that the exposure of yeast to ultraviolet rays for twenty minutes at a distance of 6 inches (15.24 cm) did not have any effect on the activity of its vitamins. R. R. Williams, however, asserted that the antineuritic factor in an aqueous yeast extract was completely destroyed by irradiation for a few hours. By spectrographic technic, Damianovich made the highly interesting observation that an active extract of yeast, although practically colorless, showed a characteristic absorption band between 2,478 and 2,600 angstrom units, which seemed to correspond to that of pyrimidine compounds.

There are unknown substances that accelerate the growth of yeast. The generic name "bios" is given to this class of substances. Bios is not necessary for the growth of yeast, but makes it grow more rapidly.

Koch and Sugata⁵² reported that the studies of Swoboda in their laboratory indicated that cystine stimulated the growth of yeast when added to certain mediums. This suggested a more intensive study on the actual utilization of various forms of sulphur in the growth of yeast. The authors reported this study in detail, finding that cystine stimulates the growth of yeast slightly in concentrations of from 1 to 4 mg per 125 cc medium, but retards it in higher concentrations. The stimulation is less than that from certain other forms of sulphur.

Kruse and McCollum, in summarizing the relation of the pellagra-preventive factor to water-soluble B, said that Goldberger and his co-workers found 1. The antineuritic factor (vitamin B *sensu stricto*) is distinct from the pellagra-preventive factor and does not in itself suffice for the growth of rats. 2. If, as some investigators have suggested, the term "water-soluble B" includes, in addition to the antineuritic factor, a so-called growth-promoting essential (possibly identical with Wildier's bios), this, like the antineuritic factor, is either inactivated by autoclaving or does not suffice by itself for the growth of the rat. 3. The pellagra-preventive factor or some associated pellagra-preventive factor (possibly the so-called growth-promoting factor) distinct from the antineuritic vitamin, though not sufficing in itself for the growth of the rat, is, in combination with the antineuritic vitamin, essential for growth in rats. Thus, Goldberger and his associates confirmed Hendrick and Smith's statement that there are two factors in water-soluble B which are necessary for the rat.

Lecoq has provisionally postulated the presence of four different vitamins of the B type in yeast: the antineuritic vitamin of Funk, the nutritive vitamin of Random and Lecoq, the antipellagrous vitamin of Goldberger and his associates and the growth-promoting vitamin of yeast of Funk and Dubin.

Kruse and McCollum concluded that where there had been one substance awaiting isolation, now one knows how many there are. At present there is no clarity in regard to the relation of the various essential components described by investigators, for instance, whether all of the thermostable factors are identical (the pellagra-preventive vitamin is thermostable), or whether the alkali-stable factor is the same as a thermostable factor. Moreover, Funk's contention that bios is related to vitamin B as an essential factor for the growth in animals must not be forgotten. This contingency presents difficulties when it is remembered that bios has been separated into three fractions.

Goldberger and Tanner thought that a deficiency of amino-acids is probably the primary etiologic factor in pellagra, although in 1920 Goldberger and Wheeler had taken somewhat more latitude in their conclusions

In relation to the production of pellagra, the dietary factors to be considered as probably essential are (1) an amino acid deficiency, (2) faulty mineral supply or constitution and perhaps (3) an as yet unknown (vitamin?) factor. As to which or what combination, or combinations, of these constitutes the specific pellagra-producing dietary defect or defects remains to be determined.

Various writers have taken exception to these conclusions. For example, Mitchell,⁷⁰ in 1924, thought that while it is clearly established that dietary error or errors of some description are primarily responsible for pellagra and that the presence of certain amounts of protein-rich animal foods, particularly milk and meat in the diet, is an effective preventive against this disease, the disease has not been definitely traced to deficiency of protein or amino-acid, "even though the arguments of the proponents of this deficiency theory are granted *in toto*." Enright²⁵ concluded "I do not mean to suggest that a food deficiency can be quite excluded, but from the facts before us it can hardly be considered as of paramount importance." Bigland⁶ and Wilson¹¹⁰ disagreed with Enright.

SULPHUR METABOLISM AND THE RELATION OF CYSTINE TO SOLAR IRRADIATION

In 1919 and 1920, Sullivan and his co-workers suggested that in pellagra the sulphur metabolism is abnormal. Cammuri, in 1910, and Myers and Fine, in 1913, reported abnormalities of sulphur metabolism in pellagra.^{46a} With a view to further consideration of this point, certain data with regard to cystine metabolism and a specific relation of cystine metabolism to solar irradiation will be reviewed.

The demands of the organism for sulphur are supplied largely by cystine.⁵³ It is necessary not only to the growth* but to the maintenance of animals (Lewis,⁵⁹ pp 401, 418 and 447). Its function in the organism appears to include an important bearing on the oxidation of tissue through the reversible cystine \rightleftharpoons cysteine reaction (Dakin¹⁹ and Lewis⁵⁹) and a detoxifying influence on certain compounds, at least one of which, cyanogen, is a product of protein metabolism.⁵⁹

Protein sulphur is present in varying proportions in different foods, as represented by its increased percentage in serum albumin as compared with casein. Under conditions of a low intake of protein, serum

* "It is obvious, however, that some amino acids, such as lysine and cystine are required in relatively greater amounts for growth than for maintenance" (Mitchell, reference 70)

albumin is more effective in maintaining nitrogenous equilibrium in dogs than is casein. However, when casein is supplemented by cystine, it is as efficient for the maintenance of the nitrogenous equilibrium as is serum albumin.

The tissues generally give a nitroprusside reaction (Lewis⁵⁹ and Lewis, McGinty and Root⁶²), but in rats on synthetic diets from which cystine was absent, nutritive failure was accompanied by an abnormally weak nitroprusside reaction in the tissues (Lewis,⁵⁹ p. 418). Definite proof as to whether the disulphide, cystine, or its reduction product, cysteine, actually exists in the protein molecule is lacking (Lewis,⁵⁹ p. 398), though the presence of cysteine is regarded as probable (Lewis,⁵⁹ p. 399).

According to Sullivan's investigations,⁹³ glutathione, a dipeptide, containing cysteine and glutamic acid, which was isolated by Hopkins (Lewis,⁵⁹ p. 415) by extraction from brewers' yeast,† gave neither the cystine nor the cysteine reaction. However, there is little apparent tendency to question the importance of glutathione in oxidative processes through the reversible cystine \rightleftharpoons cysteine reaction. Kendall⁴⁷ claimed that oxygen and sulphur are important in the promotion of this reaction. Abderhalden (quoted by Lauens⁵⁷) suggested that normally the reaction $\text{R S-S R} \rightleftharpoons \text{R SH} + \text{HS R}$ is balanced, that in "alimentarily dystrophy" (the term applied to the condition of malnutrition resulting from lack of specific substances in the diet, vitamins‡) in birds fed rice the reaction proceeds in only one direction, $\text{R SH} + \text{HS R} \rightarrow \text{R S-S R}$, reversal of the reaction is prevented and mercapto groups necessary for the oxidation are not available, and that in cyanide poisoning, the reaction can proceed only in the opposite direction, $\text{R S-S R} \rightarrow$

* A tripeptide containing cysteine, glutamic acid and glycine (Hopkins and Harris, reference 41a).

† "If the investigation of vitamin B has not yielded the desired results, its indirect effects have not been barren. While engaged in methods for isolating the antineuritic substance, Hopkins gained a discovery of equal magnitude, the separation of glutathione. Somewhat similar fortune befell several Japanese investigators in the finding of new compounds among the constituents of rice. In their search for vitamin B in yeast extract Suzuki, Odaki and Mori obtained crystals which they later identified as adenylythiomethylpentose. From the same source Odaki succeeded in separating a new thio-amino acid and several unknown bases. Funk found nicotinic acid in the vitamin fraction of rice polishings." (Kruse and McCollum, reference 54).

‡ It would appear that any condition, even though arising at an earlier period, that interferes with intestinal absorption may, under conditions favorable to the development of pellagra, result in an effective lack of the pellagra-preventive food factor. Thus the incidence of hookworm in pellagrins (Kentucky State Board of Health, reference 49, and Shelly, reference 87) or dysentery (Bigland, reference 6, and Enright, reference 25) might predispose to pellagra, and any geographical area may have a factor with a special influence on the etiology of the disease.

$RSH + HS R$, and utilization of the mercapto groups present for oxidation is not possible, since cyanides prevent conversion of the mercapto groups into disulphides. The ultimate result in poisoning caused by cyanide and in alimentary dystrophy is the same, failure of oxidation, but, as stated, the mechanism by which oxidation is prevented is different.

The excretion of urinary neutral sulphur in poisoning caused by potassium cyanide and carbon monoxide is increased.⁵³

Following the recognition of a high concentration of sulphhydryl ($-SH$) in the living part of the tissue of a tumor¹¹³ and its importance in the nuclear activity of cell division, Hammett³⁸ concluded that it is specifically essential to the nuclear processes of cell division, and that normally an equilibrium is maintained through the reversible cysteine \rightleftharpoons cystine reaction, controlled according to the law of mass action. He consistently obtained a marked intensification of the nitroprusside reaction for sulphhydryl on injury of the tips of the root, either by crushing or by scratching. Giroud and Bulliard noted an association between the concentration of sulphhydryl in the skin and keratinization, while Lightbody and Lewis⁶⁴ confirmed this principle on dietary grounds. Reimann,⁷⁹ quoting Hammett, considered that the essential difference between the nucleus of a cell in mitosis and that of a cell in the resting condition is a rearrangement of the sulphur molecules so that this element appears in the chemical group sulphhydryl. He stated that "if the sulphhydryl radical is the stimulus to cell division, the products of the reaction of sulphhydryl accumulate and stop mitosis by the time the wound is healed." These ideas led to the use of thiocresol to stimulate the healing of wounds.

The action of radiation on the healing of wounds is due, in great measure, to the influence on cell division.⁵⁷

The sulphur of cystine is readily oxidized in the body, as is also the sulphur of dipeptides containing cystine.⁵⁹ The excretion of sulphur is largely in the oxidized form of sulphates. If complete deamination is prevented, as by the feeding of phenyluraminocystine⁶² or the injection of dibenzoylcystine,⁶³ oxidation is not complete and a cysteine derivative of cystine is excreted in the urine. When cystine was injected into dogs on a diet low in protein and brombenzene was fed, an abundant synthesis of bromphenyl-mercapturic acid occurred. Cystinuria represents an "error of metabolism" which is but little understood.⁵⁹

The production of thiocyanates in the urine, as well as in the saliva, is increased after the ingestion of nitriles and certain amino-acids, and their appearance is usually considered to be due to a defensive process whereby the toxic cyanogen radicals are converted into the less toxic sulphur cyanogen compounds (Lewis,⁵⁹ p 406).

After a prolonged fast followed by the ingestion of large amounts of meat, there is a distinct lag in the excretion of sulphur (Lewis,⁵⁹ p 410), indicating either a retention of a sulphur-rich protein in the period of recovery from inanition or a much more striking lag in the elimination of sulphur than is usually observed (Wilson¹¹⁸ and Schmidt and Clark⁸⁵) Fay and Mendel stated that "the great increase in the value of the ratios during the earlier days of feeding adequate diet after starvation can be interpreted in only one way—specific retention of sulphur"

When fed to rabbits in large doses, cystine is found to be toxic⁶⁰ Wilder¹¹⁷ referred to the injurious effects of cystine on the liver and its possible etiologic influence in pernicious anemia

The high content of the epithelial protective tissue in sulphur and cystine a content greater than that of any other tissue of pure protein, suggests that the cystine may have a specific function in this tissue⁵⁹ The protective action of cystine solutions when *Paramecia* are exposed to ultraviolet radiation and the finding of Ward that cystine was the only amino-acid that had any marked absorption for ultraviolet rays have been referred to Ward called attention to the fact that the curious custom of the Arabs of wearing heavy woollen clothing may have a strong justification in the protective effect of the cystine in the wool⁴⁴

Lightbody and Lewis⁶⁴ discussed the relation of protein and sulphur content of the diet to the growth of hair in the white rat Remington⁸⁰ discussed the cystine yield and total sulphur in the hairs of various animals

Sundstroem⁹⁸ noted that a return from the tropics to a cooler climate resulted in a considerable stimulation of the growth of hair, "which growth then proceeded with seasonally determined cycles, exhibiting a maximum in June and a minimum in December" This report would seem possibly to be related to Laurens' finding of an effect of deviation from exposure to the accustomed radiant energy

Sundstroem also stated that the reports on excretion of neutral sulphur in the tropics are conflicting and do not prove an augmented catabolism of body protein in tropical man

In general, Lewis⁵⁹ held that experiments which indicate a special relation of cystine to the growth of epidermal tissues rich in sulphur (and cystine)—hair and wool—(Abderhalden,¹ Blaschko,⁷ Fuhs,²⁸ Zuntz¹²¹ and Zuntz¹²²) are interesting, but further work under more carefully controlled conditions is necessary before the specific rôle of cystine in the growth of hair can be accepted without qualification

The circumstances of excretion of creatine in the urine have been investigated rather extensively, but its significance has never been definitely determined In discussing Harding and Young's suggestion that

cystine is a precursor of creatine in the growing dog through the intermediate stages of tauine and amino-ethyl alcohol followed by methylation, combination with urea and oxidation, Lewis⁵⁹ explained

In view of the fact that creatine is determined as creatinine after dehydration in the presence of acids, and that many of the reactions by which creatinine is usually identified are also given by cysteine and mercapto derivatives, it seems possible that the variations of the creatine content of the urine observed may have been due to the presence in the urine of mercapto or other derivatives of cystine

An increased excretion of creatine by the pig has been observed after the ingestion of cystine³⁵ The increases, however, were considered to be due to acidosis resulting from the oxidation of the cystine sulphur to sulphuric acid Further observations on the occurrence of creatinuria and its possible significance will be referred to later

Hopkins isolated glutathione from yeast, muscle and hepatic tissue⁵⁹ Dakin stated¹⁹

The concentration of glutathione in the tissues is very low, but its distribution is extremely wide The blood proteins appear to contain vanishingly small amounts or possibly none, and this observation agrees with the growing conviction that scarcely any oxidation of moment occurs in this medium Yeast furnishes useful material for the preparation of glutathione though animal organs may serve equally as well

Reference has been made of the influence of sulphur as "bios" in the growth of yeast

Fay and Mendel,²⁷ in a study of nitrogen and sulphur metabolism in the dog, selected the proteins entering into the different rations on the basis of their differing sulphur content casein low in sulphur content, "meat residue," which has a slightly higher percentage of sulphur, and egg albumin, which is comparatively rich in sulphur Along with casein, beans of the genus *Phaseolus* are rated low in cystine content by Mitchell⁷⁰ Cohn¹⁶ stated that most known proteins are poor in tryptophan and cystine, nevertheless, their necessity for growth in the young, and for maintenance of nitrogen equilibrium in the adult animal is fully attested In view of the poverty in cystine characterizing proteins generally it is of interest to note its occurrence in the foods that Goldberger and his associates advocated as preventive of pellagra and to note that these foods contain cystine (or sulphur) in proportions comparable to the value for the prevention of the disease assigned them by this author

SUPERFICIAL AND REMOTE EFFECTS OF EXPOSURE TO RADIANT ENERGY

A certain protective value of pigment against the effects of exposure to solar rays as well as the necessity to regulate the degree of exposure in order to avoid definitely pathologic effects, is a matter

of common knowledge. On the other hand, it is equally obvious that pigmentation does not protect against pellagra. Only a superficial view of the matter, however, would lead to the inference that solar rays are without influence in the causation of pellagra.

It has been suggested that the dermatitis of pellagra may represent a local and superficial effect of radiation unrelated to the essential nature of the disease as a disturbance of metabolism. A variety of considerations tend to contradict this view. If it were true, pigmentation would protect against pellagra as it does against sunburn, but that it does not is shown by the relative incidence of the disease in the white and colored races in the southern United States. Again, the mortality from pellagra is higher in the white than in the Negro race. If the cutaneous lesions of pellagra represented a relatively nonessential feature of the disease and were more or less incidental to exposure to the sun, the lightly pigmented white race would probably be more susceptible to solar influence than the colored race, would more readily exhibit superficial and nonessential lesions of the skin and would be more prone to a mild and nonfatal form of the disease, and the mortality from pellagra occurring in the white race would probably be lower than that from pellagra in the Negro, however, such is not the case. The sore mouth, the diarrhea and the symptoms referable to the nervous system constitute a triad that is in itself conspicuous and a rather definite manifestation of the disease. If this triad were a matter of common occurrence independent of dermatitis, the skepticism of the most experienced clinicians with regard to "pellagra sine pellagra" would hardly exist. It is manifest that solar and ultraviolet rays have effects on metabolism not comprehended in the mere production of pigment, and that irradiation is productive of pellagrous effects more profound than dermatitis is suggested by clinical observations such as those of Enright²⁵ and the notations of Koch and Voegtlin⁵³ in their experiments on monkeys. These studies will be referred to again.

Laurens suggested that the remote effects of irradiation may be largely thermic, associated with the fact that pigmented skin holds more heat and may facilitate thermotherapy (Laurens,⁵⁷ p 14). Freund showed that the epidermis from blisters absorbed everything shorter than 325 $m\mu$, while hardened scales of skin absorbed everything shorter than 344 $m\mu$ when yellow and shorter than 329 $m\mu$ when colorless (Laurens,⁵⁷ p 10).

The process of pigmentation is essentially the deposit of melanin in the basal cells of the epidermis (Adam² and Clark¹⁵). Acquired pigment is extracellular, in contrast to its normal intracellular position as in the skin of Negroes⁵⁷. Melanin and keratin have a high sulphur

content (Koch and Voegtlin⁵³ and Lewis⁵⁹) Melanin is nonfluorescent, while epidermal keratin, white hair and sebum are fluorescent⁵⁷ Photodynamic action, however, is not proportional to fluorescence Fluorescence is the usual accompaniment, but not the fundamental cause, of the sensitization in photodynamic action, "a sort of outward and visible sign, so to speak, of an inner activity in response to light" (Clark,¹⁵ p 288) Ultraviolet irradiation is not the only influence that determines the color of the skin, other climatic factors, perhaps, being equally or more important⁵⁷ Goodale found that the natural covering of chicks is not penetrated by the effective wavelengths, and that the main receptor is the small amount of naked skin about the bird's head

Hausser and Vahle (quoted by Laurens⁵⁷) showed that the efficient wavelengths for both erythema and the formation of pigment are near 300 $m\mu$, and that the two conditions are intimately connected, pigmentation following the action of particular wavelengths only when an erythema has been produced, although a slight erythema may occur without the subsequent formation of pigment

Laurens⁵⁷ described the histology of irradiated skin as follows

The vessels become dilated with infiltration of the epithelial layer and an abnormal thickening and darkening Following intense irradiation there is sero-fibrinous or cell-rich, often hemorrhagic, exudation If the irradiation is severe enough, the collagenous tissue becomes swollen and homogeneous, the epithelium swollen and loosened, infiltrated and blistered, the loss of continuity occurring at the boundary between the granular and horny layers If the irradiation is quite intense thrombi form in the vessels of the cutis The hair follicles and sebaceous glands break down and are regenerated from the epithelium

For convenience, the cutaneous pathologic changes of pellagra as described by the Illinois Commission⁴⁶ are given here In a large number of sections studied, the general picture was that of an angio-neurotic process and resembled to a marked extent that seen in multi-form erythema The most marked change was seen in the superficial part of the corium, almost all of the infiltration occurring in the papillaris The specific observations were as follows Under low power magnification the stratum corneum appeared thickened, the stratum granulosum and rete were practically normal The upper portion of the corium showed inflammatory reaction, and the connective tissue appeared edematous Under high power, the hyperkeratosis was seen to be well marked Here and there, areas of parakeratosis were present, as evidenced by the presence of nuclei extending to the upper layer of the stratum corneum Many pigment granules were present The rete was practically normal, except in places where its integrity was interfered with by infiltrating cells Cellular infiltration was quite marked in the papillary layer, particularly

in the region of the blood vessels. Collagen and elastin were present, the former showing edematous changes. The deeper parts of the corium were comparatively normal. Elastin was absent from parts of the papillary layer.

Lewis and Zotterman have recently shown that the reactions to injury of the cutaneous vessels by ultraviolet radiation, as by freezing, burning, etc., are due to the production of vasodilator substances in the skin which diffuse into the surrounding skin and are conducted away by lymph channels.

In the "white" race, the color of the skin ranges from light bluish white or pinkish, as in the Nordic blonde or red-haired, to all shades of tan (many Mediterraneans) or brown (some Arabs, Egyptians, Abyssinians, etc.) to almost black (some Abyssinians and Hindus). "In general, the pigmentation of the races of the world varies according to the intensity of sunlight, for pigmentation appears to be primarily a protection against ultraviolet light" (Hrdlička⁴² and Huntington⁴⁴).

In this connection it may be noted that the bodily distribution of pigment in the skin presents certain anomalies not in accordance with the principle of exposure to light or other climatic influences. In the nonhairy human subject, the nipples, axillae and genitals are usually areas of relatively high pigmentation. Anatomically, if not by habit of clothing, these areas are relatively protected from the operations of climatic factors. In the dog, the hairless scrotum may or may not show an excess of pigmentation. With regard to the axillae and scrotal area of the human subject, it would appear that the loss of heat by irradiation is minimized by the anatomic arrangement, whereas by evaporation it is increased. A similar function appears to be exercised by the tongue of the dog. Sundstroem⁹⁸ noted that in mice exposed to "artificial tropics" the tails and the ears became longer and the scrota pendulous and hairless. In more recent work on rats, the rôle of an enlarged scrotum, for instance, in assisting in the loss of heat, has been proved almost beyond doubt. These considerations may have some bearing on the scrotal lesions of Goldberger's experimentally produced pellagra and experimentally produced black tongue. A tendency to development of hair is also noted in the region of these pigmented areas at the time of development of the secondary sex characteristics.

It would seem that the lesions of pellagra may appear on parts previously or habitually exposed, individually or phylogenetically, and therefore pigmented, rather than necessarily on parts exposed after a deficiency in food is instituted.

Any protective influence exercised by pigment is apparently not by virtue of impenetrability to light. Kinney observed the relative pene-

triation of light through three hands from a blonde, a brunette and a Negro respectively, which calibrated to exactly the same thickness. In both fluoroscopic and photographic tests, the penetration was greatest in the Negro, less in the brunette and least in the blonde.⁹²

It is not clear just how effects distant from the area of the skin irradiated are brought about. A mediation through the nervous system may be involved. The therapeutic results obtained in deep-seated tuberculous lesions are familiar. Lewis and Zotterman's ideas with reference to the conduction of vasodilator substances by the lymph channels have been referred to. Burchard demonstrated that irradiation no longer influenced the blood picture after pigmentation, and Rothman showed the same factor for the depression of blood pressure and blood sugar and an increase in serum calcium.⁵⁷ Buckwheat sensitizes cattle to the effects of light, but pigmentation reduces the susceptibility. Hematoporphyrin is an active sensitizer to light.¹⁵ Black and gray mice apparently cannot be sensitized to light by hematoporphyrin, while white mice can be.⁵⁷ Metallic compounds, especially sulphur and halogen compounds, show photo-electric action and are extremely phosphorescent.¹⁵

Hess, Weinstock and Helman suggested that the beneficial action of irradiating an animal is produced through the activation of cholesterol in the skin, from which it is absorbed and circulated in the blood stream.⁵⁷ Sheppard's⁸⁸ active substance in gelatins for photographic purposes (thiocyanate) went down with a condensate chiefly cholesterol, but the cholesterol was not active, and it was concluded that the active substance was dissolved only in the sterols and not chemically combined.

Laurens⁵⁷ stated that the only reasonable conclusion is that, following ultraviolet irradiation, some photochemical substance that is formed in the skin is carried by the blood stream "to these various organs, there bringing about the observed changes." Hess and his co-workers⁴¹ said that it should be remembered that in the course of activating ergosterol by means of ultraviolet radiations a series of products is formed; the sterol passes through various chemical phases, and the final product is a mixture rather than a photochemical entity.

In a "seasonally" conducted series, proof was obtained for an antagonistic behavior of the lecithin and cholesterol curves, high levels for the former coinciding with low levels for the latter, and conversely.⁹⁸

Clark¹⁵ elaborated a theory as follows. Light shorter than $300\text{ m}\mu$ acts on the living cell by ionizing its photo-electric constituents and thereby leading to photochemical action. Light longer than $300\text{ m}\mu$ acts in the same way in the presence of sensitizers which so affect the surface conditions of these constituents that their photo-electric thresh-

old is shifted into the visible, and they therefore become ionized with resulting chemical action when illuminated by visible or near ultraviolet energy

Sheppard,⁸⁸ in an investigation of the "sensitivity substance" in the gel from animal hides for the manufacture of photographic films, found that it lay in the doubly bonded sulphur as represented by allyl-isothiocyanate (mustard oil), which is believed to be derived from the food previously utilized by the animal, and that for a given emulsion and given conditions the sensitizing effect of the active body reached a maximum for a certain quantity (in the order of 1/300,000) and then decreased as the amount of the active material was increased further

When mustard oil was added to the system of the Kottmann reaction (unpublished experiments, J. H. S., 1928), it was found to alter the speed of the reaction in human serums and commercial gelatins, however, the results were not consistent. The extreme nicety of control of a variety of factors influencing the sensitivity of photographic emulsions is brought out by Davis and Withers²⁰

The considerations advanced have been chiefly in connection with normal subjects. A difference between "sick skin" and normal skin is postulated by many writers. Bovie (quoted by Laurens⁵⁷) emphasized that it is the instability of the physiologic mechanism rather than the wavelength that determines the nature of the physiologic effect produced. Clark¹⁵ traced the analogy between the photographic process and the physiologic action of light, stating that there is considerable evidence to show that diseased tissue is more susceptible to radiations than normal tissue. "To push the photographic analogy further, we may assume that normal tissue acts like a slow plate and diseased tissue like a fast one." Or, as Laurens⁵⁷ stated: "The sick organism is a much more delicate mechanism than the well, diseased tissue being more susceptible to radiation than normal, while the animal skin is an entirely different organ from the skin of man." With reference to anemia, Stewart said that under compression from surface quartz applicators or other means, the depth of penetration (of ultraviolet rays) is very much greater, probably 1½ to 1 inch (3 to 2.5 cm) according to the completeness with which the tissue is made anemic. Bernhard is convinced of the harmful effects of the lack of light on man, as exemplified in the anemic condition of those who live on the shady side of the deep valleys of the Alps as contrasted with those who dwell where they are reached by the sun's rays⁵⁷

"It has been suggested that the skin lesions in pellagra indicate a light-sensitive condition in man."¹⁵

Voegtlin¹¹² referred to this possibility in the following terms:

Raubitschek (1910) on the basis of animal experiments, advanced his very attractive photo-dynamic theory (of pellagra), which assumes that certain cereals

contain a substance which renders the skin oversensitive to sunlight. Critically viewed, none of these experiments stands the test of modern medical science.

The sites of predilection for the cutaneous lesions of pellagra are exposed surfaces. Wood¹²⁰ referred to the fact that the feet of persons who go without shoes are usually affected, and such involvement is quite common in children who go barefooted. Wood stated that he had often found lesions of the feet of women who go about the house barefooted. There would appear to be ground for the further statement that surfaces exposed during youth and the heavily pigmented genitals highly endowed for purposes of loss of heat through evaporation are not infrequent sites of pellagrous lesions, though they are not so common as habitually exposed surfaces.

In connection with an epidemic of pellagra among prisoners of war in Egypt, Enright²⁵ and Bigland⁶ commented on the distribution of the rash in relation to exposure, but they were not in entire agreement. Enright stated:

The rash is usually understood to be symmetrical. This symmetry, in my opinion, depended on the equal exposure of the affected areas to the sun's rays. If the exposure were greater for one limb there would be a correspondingly greater extent of the eruption on that side. I am quite satisfied that the distribution of the rash was directly proportional to the time and the extent of the exposure. For instance, in a rash on the chest—an uncommon site—the outline corresponded to the opening of the shirt. In the case of Turks, the rash on the feet was limited most accurately by the edges of the slippers worn. I have noticed that sun exposure intensified the eruption and that if the patient exposed himself too soon after the subsidence of an attack there was a great tendency to recurrence.

The Illinois Commission⁴⁶ found that sunlight played a part in producing or determining the location of lesions, as was demonstrated by having patients suspected of having pellagra wear fenestrated gloves, the eruption was largely limited to the exposed surfaces. However, many patients were seen who showed typical lesions occupying the hands and other usual areas and who "were not exposed to the direct rays of the sun at any time. Bedridden patients developed lesions in the same situations as those able to be out of doors."

Bigland's⁶ observations, as well as Enright's, were made in Egypt, but at a slightly different time, and in Ottoman rather than in German prisoners, as were those cited by Enright.

Bigland stated:

Though the sun's rays play an important part in the production of the rash, I was never able to make any skin changes appear at will, even after repeated trials with one arm bare or wearing a glove on one hand only. I cannot account for this failure.

Pressure areas also show definite changes in the overlying skin, which becomes rough, thick and deeply pigmented. The commonest situations for these changes

are the external maleoli, sacrum, knees, and elbows.* Thirty-five (out of sixty-four) of the cases showed these signs, and they lasted long after other typical appearances had disappeared

Bigland further described the skin of the patients in his cases

Many of the cases showed a curious fine branny desquamation over the body generally, even in the situations where a rash had not been present

One case showed a pellagrous eruption on the scrotum—interesting because this was the site where Goldberger's artificially produced pellagrins first showed the rash

* Cowgill, Stucky and Rose, 1928 (reference 18), have observed the formation of ulcers on various bony prominences, particularly on the limbs, of many of their dogs subsisting on diets adequate except for vitamin B

The remarkable symmetry in distribution of these ulcers and the fact that they were produced in animals fed on carefully controlled diets are points worthy of note. In some of their animals that were placed on the deficient diet twice, the "complete" ration being fed in the intervening period, these lesions developed twice, associated each time with the defective diet, and disappearing when vitamin B was administered. The absence of the cardinal signs of inflammation in these ulcers further indicates their malnutritional origin

Even at the cost of digression from a subject involved, at best, the analogy presented by psoriasis in the confused etiology and others of its aspects as compared with pellagra attracts attention. Schamberg (reference 83) referred to psoriasis as an affliction which has been known since the days of the early Greeks. It appears to have certain features in common with pellagra and others of an opposite character. The similarities are more or less obvious. It appears to be opposite in age incidence, sex incidence, seasonal incidence and in the value of a diet low in protein. Hebra was in the habit of stating that patients with psoriasis are "blooming healthy individuals," and he regarded the disease as a "morbus fortium"

Outbreaks are influenced by seasonal conditions. In the climate of Philadelphia (Schamberg, reference 84), the vast majority of patients are better in summer and worse in the cold seasons. Recurrences are not uncommon with change of season in spring and fall. Psoriasis is but rarely seen in the Orient and in the tropics

In terms of Hammett's studies, nuclear cell division is overactive, and on Hammett's principle the —SH group would be regarded as overactive. Hammett's ideas grew out of the finding that the metal lead specifically retards proliferation of the cells, and he was led to the conclusion that the metal, by precipitation, removes from activity some compound essential to the reproduction of cells. Schamberg quoted the opinion of Throne and Myers (reference 100) "Sodium thiosulphate is of no value in the treatment of patients whose blood does not show the so-called 'metallic picture', that is, a high sugar and a low chloride content, but is of great value in those cases showing the metallic picture. In cases in which the disease process is present in large sheets or in which it is universal, they found its action helpful. Nail involvement has also responded to this line of therapy. The action of sodium thiosulphate in these cases is in removing the retained metal from regions in which it has been precipitated and in reacting it"

Lastly, under this heading I wish to describe a condition to which only one reference could be found (Marie). In eight of the cases there was noted a peculiar seborrheic condition, chiefly around the alae nasi, sometimes scattered over the whole face. In appearance this condition was likened to small sulphur granules raised above the surface of the skin. This was not found among non-pellagrous Turks.

In pellagra, outside of the cutaneous lesions, pigmentation has been described histologically in the medulla (Bigland,⁸ p 950, and Warnock at Abbazia), in the cortical cells of the brain, in the adventitia of the smaller vessels, in the peripheral ganglions, both spinal and sympathetic (Tuczek in 1893⁵³), and in the intestinal mucosa. Lynch (quoted by Wood¹²⁰) described the characteristic appearance of the intestinal mucosa of the pellagrian as "the flattened, deep red or bronzed, thickened mucosa, with shallow, irregular mucosal ulcers."

THE THEORY OF A DEFICIENCY OF FOOD AS THE CAUSE OF PELLAGRA

It is not necessary to review the elaborate data on which the advocates of this theory, especially Goldberger and his associates, have based their conviction of its soundness. Though there are considerations that lead to serious question as to the sufficiency of their views, the relatively high incidence of the disease in the economically underprivileged classes,* the experimental observations, the epidemiologic studies and the measure of therapeutic success that has attended the curative and especially the preventive practice of their principles attest a genuine and fundamental influence of the factor of a deficiency of food. Goldberger and his co-workers have not attempted to state the exact nature of the deficiency, though they consider that it is probably a deficiency in amino-acids.

Wood¹²⁰ thought that it is reasonably certain that if the peasant class were provided with a generous, well balanced and varied diet, the ravages of pellagra would stop, but he regarded such a procedure as "eminently impracticable" at this time. Taylor, in his revision of Wood's article, was inclined to regard an infectious agent as also operative, but he did not question the importance of a deficiency of food.

If the essential feature of a deficiency of food is one of amino-acids, the deficiency would seem probably to be related to the recognized general limitation of the intake of protein characteristic of warm climates generally, being emphasized with the seasonally recurring

* However, the economically underprivileged classes, among the rural population at least, by reason of occupation are more definitely subject to whatever influences there may be in climatic conditions (Vance [reference 110] and many others).

temperature of summer. In this sense, the deficiency might be either in the nature of a specific lack or in the nature of a lack of stimulus to the oxidative processes of metabolism belonging to proteins generally and to certain amino-acids in special degree, which is described under the term "specific dynamic action." Such an explanation, if found to be tenable, would harmonize with the tendency so far observed in the South for the metabolic rate to decline as summer approaches, and would not be inconsistent with the view that the decline in metabolism is contributed to also by a relatively high exposure to the solar rays of summer as compared with the exposure during winter, and further would not be inconsistent with the view that any cause operating to lower the basal metabolism in this geographic area in summer favors the development of pellagra. A direct influence of solar light, without referring this influence through the intermediation of the intake of protein or the composition of food, would seem to be suggested by the rather sharp upper border of the pellagra belt and the improbability of a correspondingly sharp line of demarcation in food habits.

While the preventive and curative action of yeast as described by Goldberger may be referable to the power of yeast to increase the basal metabolism, the substitution of yeast for thyroid substance has not seemed to maintain the metabolic rate of persons with depressed metabolism in any consistent way (J H S.)

If the beneficial effects of the diet recommended by Goldberger are attributable to the effect on general metabolism, the claims that have been advanced for thyroid medication in the treatment for pellagra (Shelley⁸⁷ and Smith⁹¹) would be referable to the same mechanism.

The relative freedom of the tropics from pellagra would seem to point to the fact that neither a lowered basal metabolism nor a low intake of protein can be the essential cause of pellagra. While these conditions doubtless favor its development, more specific factors are apparently involved. It is possible that there is a combined effect of lack of a specific dynamic action of foods containing protein and the positive effect of exposure to solar rays. Even so, a deficiency in the intake of protein may be important in respect to a specific factor, such as cystine.

With reference to the various claims for an etiologic influence of alcoholism and of bacterial, parasitic and other pathologic states of the gastro-intestinal tract, if such conditions interfere with the absorption of the essential factor concerned in the deficiency of food in pellagra, these are merely modes of development of the deficiency of food, and their recognition, without assuming for them a specific toxic or infectious influence, involves no conflict with the views of those who hold to the idea of a deficiency of food as a usual and important cause of pellagra.

Similar accommodation of seemingly opposed views with reference to a deficiency of iodine in the etiology of endemic goiter has been suggested by several writers

METABOLISM IN PELLAGRA

The chemical studies of pellagra described in the literature concern chiefly the metabolism of nitrogen, sulphur and the lipoids. The supply of sulphur, chiefly cystine, for the normal organism and its metabolic course within the organism, as far as is known, are so closely bound up with nitrogen that usually it is not possible to separate distinctly their respective rôles^{*}

According to Folin, the absolute quantity of creatinine eliminated in the urine of a patient on a meat-free diet is a constant quantity differing for different persons, but wholly independent of quantitative changes in the total amount of nitrogen eliminated. In pellagra, the failure of the creatinine coefficient (ratio of excretion to body weight) and of the excretion of thiocyanate (also of gastric acidity¹¹²) to return to normal with the return to normal of total nitrogen in the convalescent or cured pellagrian appears to indicate that restoration of a normal exogenous metabolism is not immediately, at least, accompanied by restoration of a normal endogenous metabolism.

Folin⁵⁹ found that in patients on diets relatively high in protein the normal distribution of urinary sulphur is organic, 87.8 per cent, ethereal (conjugated), 6.8 per cent, and neutral (unoxidized), 5.1 per cent. In general, the excretion of neutral sulphur is regarded as definitely characteristic of endogenous metabolism as is the excretion of creatinine. In pellagra, however, it appears that when the creatinine coefficient is low, the excretion of neutral sulphur is increased, as in poisoning caused by cyanogen.

The chief features of the metabolism of pellagra,⁹⁷ many of which are proportioned to the severity of the disease, are as follows:

The general metabolism, as measured by the consumption of oxygen or the excretion of carbon dioxide, is low.

The exogenous and endogenous metabolism, as measured by the urinary excretion of nitrogenous fractions, is low.

There is an abnormal mineral metabolism, as is evidenced by a low excretion of phosphorus pentoxide.

The utilization of protein is regarded as being somewhat depressed⁹⁷ though the observations made in Egypt did not indicate this.

^{*} "We must conclude from an extensive study of the N/S ratio that this is an expression of such complex metabolic relationships as to make any idea of judging by it the nature of tissue undergoing metabolism during fasting fatuous. The most significant point, it seems, is that the relative excretion of N and S in the urine is an individual metabolic response" (Morgulis, reference 71).

There is a decrease in the thiocyanate contained in the saliva, but the normal diastatic power of the saliva is average ⁹¹

Gastric anacidity is common, and hypo-acidity is usual

Intestinal putrefaction is increased (Sullivan, Stanton and Dawson ⁹⁷ and Veddei ¹¹¹), but the phenols in the urine were not found to be materially altered quantitatively ⁹⁵

The cholesterol content of the blood is increased * ⁷⁷

The albumin-globulin ratio was reported normal in 1 case † ⁸²

Hematoporphyrin is not present in the blood serum ⁸⁶

The alkali reserve of the blood is normal ⁹⁶

The cyanide detoxifying power remains unimpaired, provided the supply of cystine is adequate ⁸

The total amount of nitrogen in the urine is low ⁹⁷

The ratio of urea is "low enough to suggest liver insufficiency" ⁹⁷

The uric acid content is low

The creatinine coefficient is much below normal and remains low during convalescence. It is low in proportion to the severity of the disease as manifested clinically ⁹⁷. A report on the excretion of creatine has not been observed.

The excretion of thiocyanate is low as compared with the content of the urine at the time of the patient's discharge as being cured, but the increase during convalescence is not proportional to the increase in the total content of nitrogen ⁹⁴

Voegtlin ¹¹² found the amounts of ethereal sulphates, neutral sulphur, hippuric acid (Murlin, 1920) and indican increased. He regarded the purin metabolism as being normal.

Acetone and diacetic acid are not found ⁶

After a curative diet, the products of exogenous metabolism rise to approximately normal ⁹⁷

Human milk does not show chemical changes that are considered to account for the disease in nursing infants ¹¹²

In 5 cases of uncomplicated pellagra, as compared with normal controls, extensive chemical analyses of the central nervous system revealed the following principal abnormalities ⁵³

"It seems not improbable that changes in the globulin-albumin ratio in plasma may have something to do with variations in sterol (cholesterol) content of plasma in disease, and even under normal physiological conditions" (Gardner and Gainsborough, reference 29)

† "Recent experiments in this laboratory show that a dilute solution of egg albumin may be changed so as to react like globulin towards ammonium sulphate after an hour's exposure, in a quartz test tube, to the light of a quartz mercury arc at a distance of 5 cm" (Clark, reference 15). However, Handovsky reported a seasonal variation in animals, with albumin relatively higher in summer and globulin in winter (Lovett, reference 65)

The water tended to increase, there was a loss of lipoids and the proteins tended to decrease slightly

There was a decrease in the cerebrosides, phosphatides and sulphatides, which is probably due to an increased lipolytic process associated with the degeneration of the tissues

There was a relative increase in the cholesterol content of the cerebellum and the spinal cord

The cholesterol in the cerebrum was diminished

The proteins seemed to be the least affected of all the constituents. They were present in normal amounts in the cerebrum and cerebellum. In the spinal cord, a decided increase was noted in the dry tissue, whereas in the fresh tissue the proteins were decreased

There was considerable increase in extractives, which compensated for the loss of lipoids, the nitrogen-containing, noncolloidal extractives were especially responsible for the increase in extractives

There was a loss of neutral sulphur in the cerebrum and spinal cord and an increase in this constituent in the cerebellum, "which may possibly be interpreted as a disturbance of the oxidative power of the colloidal sulphur compounds"

In a general way the spinal cord exhibits the most striking chemical changes, a fact which is in perfect agreement with histological observations (compare with Singer and Pollock, reference 90). The chemical changes in pellagra, while similar in many respects differ from those of other diseases affecting the nervous system

The present investigation brings out the fact that the central nervous system in pellagra is subjected to a series of considerable chemical changes involving principally certain lipoids. The study of these changes from a chemical point of view has led to a new method of characterization of this disease, which may permit to correlate them, as has been shown in the preceding investigation, with the changes experimentally produced in the nervous system of animals

The digestive secretions^{11,2} show some definite, although not constant, deviation from the normal. In regard to gastric secretion (Hunter, Givens and Lewis, 1916), it was found that a large number of, though not all, pellagrins suffer from anacidity and lack of pepsin. Free hydrochloric acid may be increased, normal, decreased or absent. Pepsin is absent in cases of anacidity. Children are affected in the same way as adults (Givens, 1918). There does not seem to be a relation between the severity of the disease and the degree of gastric disturbance. In some cases with anacidity and lack of pepsin, the administration of hydrochloric acid by mouth results in the secretion of pepsin

It is interesting to call attention to several cases with anacidity which, as a result of the dietary treatment, had lost all clinical symptoms of the disease, and yet had not shown a return of the gastric secretion to normal even after several

months This points to a more or less permanent damage to the secretory apparatus, which may possibly find its explanation in a permanent anatomical change either of the nervous innervation of the gastric glands or in the glands themselves

There are certain indications that the excretion of the amino-acid nitrogen is increased in cases with gastric anacidity (Murlin, 1920), an observation which points to an imperfect cleavage of proteins in the absence of gastric digestion The neutral sulphur fraction of the urine is also increased

Abderhalden and Wertheimer (quoted by Lewis ⁵⁹) found that when the muscle of a frog was digested with pepsin and hydrochloric acid, the digest soon gave a strong nitroprusside reaction for mercapto groups That the appearance of this reaction was due primarily to the activity of the pepsin was shown by comparative tests in which muscle was digested with hydrochloric acid alone If the peptic digest was treated with alkali, the nitroprusside reaction became weak, and the addition of active trypsin did not restore the reaction to its former strength As a result of these observations, Abderhalden suggested "dass Pepsin und Trypsin das Eiweissmolekul an verschiedenen Stellen angreifen Pepsin sprengt vielleicht S-S Bindungen unter Bildung der Gruppen SH, SH" (that pepsin and trypsin attack the protein molecule from different points Perhaps pepsin decomposes S-S compounds under formation of SH, SH groups)

Lewis continued Similar observations have been made by Harris Egg white, which reacted negatively with nitroprusside and ammonia, gave strongly positive reactions as digestion with pepsin-hydrochloric acid proceeded Fractionation of the digest by precipitation with ammonium sulphate showed that the proteoses, peptones and polypeptides all contained a group reactive to nitroprusside Under anaerobic conditions, the nitroprusside reaction given by the digest persisted for several months, but in the presence of air even in an acid solution, the reactivity disappeared in a few hours, and even more rapidly in alkaline solution During tryptic hydrolysis of egg white, the nitroprusside reaction was not observed at any stage of the hydrolysis This might have been due to the fact that oxidation of the mercapto groups is favored by an alkaline reaction, a condition necessary for effective digestion by trypsin

No studies of the sulphur (and cystine) content of the products formed at different stages of peptic, tryptic and ereptic digestion of sulphur-rich proteins have been made in which the newer analytical methods for proteins and amino acids have been employed Such an investigation should throw considerable light on the problem under discussion

A rickets-producing diet caused a definite rise in the p_H of the contents of the intestines even to alkalinity in dogs (Grayzel and

Miller), and ultraviolet irradiation (or the administration of cod liver oil) changed the reaction to the normal range, the gastric contents showing no change ⁵⁷

GOLDBERGER AND WHEELER'S EXPERIMENTAL PELLAGRA IN WHITE
MALE CONVICTS (IN MISSISSIPPI, 1920) ³¹

Goldberger and Wheeler concluded that pellagra developed in at least six of their eleven volunteers as a result of the diet on which they subsisted. The relative influence of diet and solar light was apparently not taken into account in their experiment. The period during which the volunteers subsisted on the experimental diet was from April 19 to October 31, inclusive. The volunteers continued to do a share of the work on the farm, but when compared with the convicts used as controls they had shorter hours of work and regular periods of rest when in the field. They probably did not rest in the sunlight, and their exposure to light was therefore less than that of the controls and less than that of other farm laborers.

The earliest date of the beginning of a cutaneous eruption was September 12, about the end of the fifth month of the diet, or about three months after the development of certain subjective symptoms. All of the subjects lost weight, and the loss of weight was particularly marked after the development of the eruption. In the six subjects in whom the eruption developed, the initial site was the scrotum. Later, in one subject classic lesions developed on the hands and in another on the neck. In comparison with pellagra that develops spontaneously, it may be noted that (a) The diet was probably a rather extreme example of the supposed pellagra-producing diet. (b) Though the season was favorable to maximum intensity of solar light, the exposure was somewhat less than that under normal working conditions on a farm. (c) Exposure during the previous winter was presumably the average of other convicts on the same farm. (d) All of the subjects lost weight, whereas the excellent general state of nutrition is a paradoxical feature of pellagra frequently commented on* (Goldberger and

* Generally speaking, during fasting, the basal metabolic rate is lowered along with the loss of weight, whereas in beriberi and in normal persons (Okada and his co-workers, reference 76), with vitamin B starvation and an adequate amount of carbohydrate, protein and fat, the basal metabolic rate is lowered without loss of weight and with even a gain in weight. According to these observers, the basal metabolic rate is increased by vitamin B.

In a series of limited observations, I found that the administration of yeast is followed by some increase in the basal metabolic rate, however, in a case of myxedema which responded by elevation of the basal metabolic rate under medication with thyroid both before and after the feeding of yeast, an increase in the basal metabolic rate was not noted during the administration of yeast over a period of two weeks.

Wheeler³²) (e) The lesions of the skin appeared primarily and chiefly on the genitals, which, especially in the male, is a relatively rare site

Goldberger and Wheeler^{*} suggested that the site of at least the initial dermatitis is bound up with a specific quality of the diet. If it is assumed that in the etiology of pellagra dietary deficiency is a usual and important factor and that exposure to the solar rays of summer following relatively little exposure to these rays in winter is a usual and important factor, it would be inferred that the results obtained by Goldberger and Wheeler represented an instance of exaggerated influence of a dietary deficiency as compared with the influence of solar light, and it would be suggested as a possibility that this imbalance in causation determined the site of the major cutaneous lesions on the heavily pigmented, unexposed genitals, which are highly endowed as to function for the loss of heat through evaporation. Such an idea would receive some support from the relative frequency of genital lesions in the relatively housed female^{*}

EXPERIMENTAL BLACK TONGUE OF DOGS AND ITS RELATION TO PELLAGRA³²

A synonym for black tongue is "southern canine plague." In the United States the disease is confined to the area of endemic pellagra, and Goldberger and Wheeler considered that their experimental results established "well nigh conclusively" an identity of the two conditions black tongue and pellagra. The single important difference these authors noted in the condition they succeeded in producing experimentally in dogs as compared with spontaneously arising black tongue was that, while no eruption on the external genitalia of the female dog was observed, an eruption developed on the scrotum in about 40 or 50 per cent of attacks in the male dog. Such an eruption, these authors stated, seems never to have been recorded in black tongue.

It is not possible to compare the epidemiologic features of black tongue in the male and female dog in the same way the epidemiologic features of pellagra may be compared in the different age groups of the two sexes in the human subject. However, as in the experiment on pellagra of these authors, it is to be noted that (a) The diet was probably a rather extreme example of the supposed black tongue-

^{*} Torraca, at the Mosso Institute, studied the relative effects of sunlight, shade and bandaging on the artificially inflicted wounds of guinea-pigs. The best results were obtained with the animals whose wounds were bandaged and kept in sunlight, while the wounds that were freely exposed to sunlight healed more quickly than those kept in the shade. The wounds were aseptic, so that the influence was not bactericidal (Laurens, reference 57)

producing diet (b) Though the season was favorable to maximum intensity of solar light, the dogs were apparently housed in kennels inside the laboratory, which was located at the extreme upper edge of the black tongue belt (Washington) (c) The scrotal lesions produced in the male dog have not been recognized in the spontaneously occurring disease

If it is assumed that in the etiology of black tongue dietary deficiency is a usual and important factor and that exposure to the solar rays of summer following relatively little exposure to these rays in winter is a usual and important factor, it would be inferred that the results obtained by Goldberger and Wheeler represent an instance of an exaggerated influence of dietary deficiency as compared with the influence of solar light, and it would be suggested as a possibility that this imbalance in causation determined the site of the lesions on the scrotum. Such an idea would receive considerable support from the failure of all observers to note scrotal lesions in the spontaneously developing disease.

Whatever may be the explanation, the predilection of the cutaneous lesions for the genitals in both experimental pellagra and experimental black tongue, in contrast to the conditions in these diseases when they arise spontaneously, is a notable feature of the reports of these investigators.

The heat regulatory function of the dog's tongue has already been referred to, and Sundstroem's observations on the function of elongation of the scrotum under experimental conditions has also been alluded to. The conspicuous lesions of experimental black tongue occurring in these organs and the conspicuous lesions of pellagra occurring in the skin and in the experimentally produced condition, on the scrotum, the skin being the tissue chiefly concerned with the regulation of heat in the human subject, are suggestive of a metabolic disturbance common to the organs of the loss of heat in black tongue and pellagra, respectively.

An identification of black tongue with pellagra would seem to minimize to some extent the importance of economic factors in the production of the latter disease, for though the dog shares in large measure with his master, his food habits are not altogether dependent on those of his master and he enjoys a certain freedom to roam and forage according to his natural tastes and instincts.

COMPARATIVE DATA ON PELLAGRA AMONG PRISONERS OF WAR IN EGYPT

Enright,²⁵ in 1918, and Bigland,⁶ in 1917, observed approximately the same number of pellagrins among prisoners of war at Cairo, Egypt,

the former Germans and the latter Ottomans. They came to radically different conclusions in regard to the influence of diet in the causation of the disease. No data are available by which a comparison can be made of previous exposure to light, nor of the relative exposures about the time the disease appeared in the two groups, respectively. However, the disease developed in both groups while the prisoners were in "the Cairo district" (Cairo, Heliopolis and Maadi), and the two groups were observed at Cairo. The seasonal incidence is clearly recorded and can be compared with the pyrreheliometric measurements at Cairo (Helwan)[†] (table 2)⁵⁰

The pyrreheliometric observations were for the period from February 1914, to December, 1923. Thus they include the period of pellagra morbidity under discussion, but they represent average figures for the period of observation and do not cover specifically the periods of the outbreaks of pellagra. It will be noted that, with the air mass held constant, the curve of the measurements corresponds closely with

TABLE 2—*Incidence of Pellagra Compared with Pyrreheliometric Measurements*

	Nov	Dec	Jan	Feb	March	April	May	June	July	Aug	Sept	Oct
Germans, 1918			13	11	12	14	4	2	7			
Ottomans, 1916-1917	1	5	23	12	10	4	Un known	9				
Pyrreheliometer	1.23	1.27	1.31	1.28	1.22	1.16	1.13	1.12	1.13	1.15	1.17	1.19

that of the monthly incidence of pellagra, especially among the Ottomans. The observation would hardly be of significance unless supported by other data involving the same principle.[‡]

* Vedder (reference 111), who was invited by the Thompson-McFadden Pellagra Commission to investigate the dietary deficiency phase of pellagra in connection with the study of the commission (reference 89), found little evidence to support the theory of a deficiency of animal protein as the essential cause of pellagra. Vedder noted "that of the 82 persons in families using fresh meat daily, four, or 4.88 per cent were pellagrins, of the 2,591 individuals in families using this food habitually, 3.74 per cent were pellagrins, and of the 263 persons never using fresh meat only four, or 1.52 per cent, were pellagrins. Similar figures were obtained with regard to the use of eggs."

† "The pigmented appearance of the involved skin varies in different races, and in Caucasians it differs greatly in blondes and brunettes. The Egyptian shows the pigment deposit much more than the American and more than the negro, not because of a lesser degree of pigment but because of the peculiar contrast which possibly may be due to peculiar rays of intensity in the Egyptian sunlight" (Wood, reference 120, p. 352).

‡ The seasonal incidence of pellagra in the Armenian refugees at Port Said corresponded more nearly to that of the southern United States. The refugee population consisted of 4,058 men, women and children, and the customary predominance of female pellagrins (79 per cent of 653 cases) was noted. Of the 470 women and children captured with the Ottomans and brought to the neighborhood of Cairo, none contracted pellagra. Data are not available for comparing the seasonal incidence at Port Said with climatic conditions (reference 56).

The difference of opinion between Enright and Bigland in regard to the influence of diet is of interest in connection with the following comparison

Sullivan and his co-workers⁹⁷ considered that their hospitalized patients could be divided into at least two rough classes (1) those with marked symptoms of the skin but otherwise not much physical deterioration, a class that may be called dermal, and (2) those with moderate or slight symptoms of the skin but with general weakness, paresthesia and marked intestinal upset, a class that may be called systemic. The former showed evidences of being relatively mild. Thus a rough grouping may be made: systemic type, severe, dermal type, mild.

TABLE 3—*Relative Influence of Dietary Deficiency and Positive Exposure to Sunlight in the Etiology of Pellagra and Black Tongue*

	Spontaneous Pellagra	Goldberger's Convicts
Dietary deficiency	++	+
Positive effect of light	++	0
Mouth and tongue	++	0
Scrotum	++	+
Mortality	Average	? if continued
	Spontaneous Black Tongue	Goldberger's Dogs
Dietary deficiency	++	+
Positive effect of light	++	0
Mouth and tongue	++ (name)	+
Scrotum	0	++
Mortality	Average	+ when continued
	Enright (Germans)	Bigland (Ottomans)
Number	65	64
Dietary deficiency	0	+
Positive effect of light *	+	0
Mouth and tongue	-- ("usually")	++ (29)
Scrotum	0 (none mentioned)	++ (1)
Mortality	15% (65/1)	37.5% (64/24)

*Data were not available for comparison of the intensity of light in 1917 and 1918

If the relative influence of dietary deficiency and positive exposure to sunlight in the etiology of pellagra and black tongue is allowed to remain an open question for the purpose of comparison, and if Goldberger and Wheeler's description of their experiments with convicts and dogs is taken into consideration, table 3 appears to be expressive of the relative play of the two etiologic factors and the relative results in respect to certain symptoms and mortality in the groups with spontaneous pellagra and the volunteer subjects in whom the disease was produced experimentally and in spontaneous black tongue and the dogs in which the disease was produced experimentally. In the comparison between the German and the Ottoman prisoners, the difference of opinion between Enright and Bigland has been referred to, and

there is the further interesting difference in their observations on the direct influence of exposure to light in the production of lesions on areas of the skin so exposed

In each of the three comparisons (table 3) it would seem that when dietary deficiency is obvious and outstanding in comparison to exposure to light, the effect partakes of Sullivan's systemic type rather than his dermal type, dermal effects readily attributable to direct exposure of the affected parts to light are at a minimum, scrotal lesions are relatively high, and mortality, where it can be compared, is great.

KOCH AND VOEGTLIN'S EXPERIMENTS WITH A RESTRICTED VEGETABLE DIET IN MONKEYS

Reference has been made to the study of Koch and Voegtlin⁵³ of the chemical changes in the central nervous system in pellagra and

TABLE 4—*Distribution of Sulphur, Phosphorus and Nitrogen**

		Percentage Variation from Normal Sulphur				
		Protein	Lipoid	Neutral	Inorganic	Total
Monkey	encephalon, fresh tissue	— 6	—32	—40	—33	—18
Human	cerebrum, fresh tissue †	± 0	—31	—18	± 0	—10
Human	spinal cord, fresh tissue, mean ‡	— 5	—26	—15	—25	—16
		Extractive				
Monkey	spinal cord, fresh tissue, mean	—11	—18	— 9		—14

* Only the sulphur fractions are quoted here

† Comparison of two normal cases with five cases of pellagra

‡ Comparison of four normal cases with five cases of pellagra

their notation of an agreement between their findings and the histologic changes observed in this condition. In connection with that study, the investigators carried out experiments on rats and monkeys, observing the chemical and histologic changes in the central nervous system as a result of the restricted vegetable diet. They noted that, in general, the changes observed corresponded somewhat closely to those observed in pellagra, in some instances, however, a considerable difference was noted. The histologic changes were similar to those found in pellagra. In their extensive investigations, the percentage of variation of sulphur from normal was studied, and the general agreement in the experimentally produced condition and in pellagra is seen in the comparison given in table 4.

The authors did not make any reference to exposure of the rats to light, nor did they ascribe any significance to the exposure of the monkeys to sunlight, nevertheless, their tables (tables 5 to 11) clearly show the extent of exposure of the monkeys.

TABLE 5—*Monkey M I*

Diet	Corn oil cake, 100 Gm daily	Began feeding March 14, 1914	Body weight, 3.1 Kg
Date	Body Weight	Comment	
March 21	2.84		
27	2.66	Intense diarrhea	
April 3		Intense diarrhea	
11	2.48	Intense diarrhea	
18	2.43	Looks depressed very weak	
22		Exposed to sunlight for 3 hours	
24		Coughing	
25	2.42	Diarrhea still persists	
27		Exposed to sunlight for 3 hours	
May 2	2.30		
6-7		Exposed to sunlight for 3 hours, blood vessels of ears greatly dilated	
9	2.33	Diarrhea persists	
11		Exposed to sunlight for 6 hours	
12		Exposed to sunlight for 3 hours	
15	2.28	Tongue coated, otherwise normal, exposed to sunlight for 3 hours	
19		Exposed to sunlight for 3 hours	
20		Diarrhea persists	
20		Two erythematous spots in region of external canthus, nose shows erythematous spots, animal rubs nose with hands as if irritated	
		Exposed to sunlight 1 hour, coughs	
21	2.09	9 a m, redness has much increased since yesterday, coughing, intense diarrhea, died at 1.30 p m while exposed to sunlight	

TABLE 6—*Monkey M II*

Diet	Corn oil cake no 2 (Indianapolis), 100 Gm daily	Began feeding March 20, 1914	Body weight, 3.68 Kg
Date	Body Weight	Comment	
March 20		Animal has diarrhea	
21	3.30	Animal has diarrhea	
27	3.32		
April 2	3.12	Animal has diarrhea	
3	3.07	Animal has diarrhea	
18	3.00		
22		Exposed to sunlight for 3 hours	
24		Diarrhea continues	
25	3.05	Diarrhea continues	
27		Exposed to sunlight for 3 hours	
May 2	3.00	Diarrhea continues	
7		Exposed to sunlight for 3 hours	
9	2.92	Diarrhea continues	
11		Exposed to sunlight for 6 hours	
14		One hard boiled egg added to diet	
15	2.89	One hard boiled egg added to diet	
16		Diarrhea, tongue and gums normal	
19-21		Exposed to sunlight every day, estimated 3 hours daily	
23	2.66	Diarrhea continues	
26	2.40	Edema of upper right eyelid	
31		Subcutaneous hemorrhage on upper right eyelid, is very weak and looks depressed, exposed to sunlight for 30 minutes	
June 4		Abnormal redness of gums	
6		Animal unable to walk intense diarrhea, died at 3 p m	

TABLE 7—*Monkey M III*

Diet	Equal parts of corn meal and sweet potatoes (cakes)	Began feeding May 5, 1914	Body weight 2.5 Kg
Date	Body Weight	Comment	
May 9	2.32		
11		Exposed to sunlight for 6½ hours	
12		Exposed to sunlight for 3 hours	
15		Exposed to sunlight for 3 hours	
16		Animal has diarrhea	
19		Exposed to sunlight for 3 hours	
20		Exposed to sunlight for 1 hour	
21		Exposed to sunlight for 2½ hours	
22		Exposed to sunlight for 1½ hours	
23	2.38		
29	2.42		
June 5		Exposed to sunlight for ½ hour	
6	2.39		
13	2.39		
19	2.28		
26	1.87	Exposed to sunlight for 15 minutes	
27	1.86	Had been well up to today, is sick now cannot be roused from lying position, marked stupor, died at 9 p m	

The data do not permit an estimation of the intensity of light to which the animals were exposed, for though the day of the year is given and the air mass is calculable, other factors, including the hour

TABLE 8—*Monkey M IV*

Diet	Yellow corn meal (cakes)	Began feeding May 3, 1914	Body weight 2.27 Kg
Date	Body Weight	Comment	
May 5	2.27		
11		Exposed to sunlight 6½ hours	
12		Exposed to sunlight 3 hours	
15	2.18	Exposed to sunlight 3 hours	
19		Exposed to sunlight 3 hours	
20		Exposed to sunlight 1 hour	
21		Exposed to sunlight 2½ hours	
22		Exposed to sunlight 1½ hours	
23	2.12		
29	2.07		
June 5		Exposed to sunlight ½ hour	
6	2.15		
13	2.04		
19	1.95		
25		Animal has sick appearance and diarrhea	
26	1.73	Exposed to sunlight 15 minutes, lies down most of the time, looks depressed	
27		Cannot be aroused from stupor	
28		Died at 1.45 p. m.	

TABLE 9—*Monkey M V*

Diet	Yellow corn meal (cakes)	Began feeding May 3, 1914	Body weight 2.8 Kg
Date	Body Weight	Comment	
May 9	2.73		
11		Exposed to sunlight for 6½ hours	
12		Exposed to sunlight for 3½ hours	
15	2.61	Exposed to sunlight for 3 hours	
19		Exposed to sunlight for 3 hours	
20		Exposed to sunlight for 1 hour	
21		Exposed to sunlight for 2½ hours	
22		Exposed to sunlight for 1½ hours	
23	2.56		
29	2.56		
June 5		Exposed to sunlight for ½ hour	
6	2.50		
13	2.49		
19	2.38		
25		In good condition, lively	
26	2.21	Exposed to sunlight for 15 minutes	
28		Appears sick, lies on the floor, difficult to arouse	
29		Depressed, exposed to sunlight 1 hour	
30		8 a. m., in dying condition, 9 a. m. dead	

TABLE 10—*Monkey M VI (Control)*

Diet	Bananas, eggs, sunflower seeds, carrots, Irish potatoes and wheat bread	Body weight 2.89 Kg
Killed Sept. 16, 1914, by means of chloroform		
Neeropsy		
No pathologic changes noticed	Weight of fresh brain 81.59 Gm	

of the day, are lacking. If the data are redistributed so as to show the average number of hours per day of exposure and the elapsed days before the death of the monkeys, the data in table 12 are obtained.

In table 12 and chart 1 an inverse correlation is noted between the hours of exposure and the duration of life. The first animal survived

longer than the total exposure would indicate as probable. This was at a time of the year when the air filter was relatively great as compared with that when the other animals, except M II, were subjected to experimentation, but the significance of this is uncertain. Animal M VII

TABLE 11—*Monkey M VII*

Diet	Raw carrots	Body Weight	Began feeding May 23, 1914	Body weight 2.5 Kg	Comment
May	23	2.50			
	29	2.40			
June	5		Exposed to sunlight ½ hour		
	13	2.35			
	19	2.28	Feces soft, color of carrots		
	26	2.30	Exposed to sunlight 15 minutes, skin of face shows yellowish tinge		
	28		In good condition, lively, exposed to sunlight 1 hour		
July	2		Diarrhea, skin shows marked yellow tinge		
	3	2.21	Fed sunflower seed by mistake		
	10	2.15			
	14		Diarrhea		
	17	2.17	Diarrhea persists		
	25	2.09			
Aug	1	2.07			
	8	2.05			
	15	2.04			
	21	2.02			
	29	2.06			
Sept	5	2.16			
	11	2.02			
	15		Diarrhea persists		
	19	2.02			
	27	2.06			
Oct	1		Fed bananas by mistake		
	5	1.84			
	10	1.62			
	18	1.58			
	24	1.60			
	31	1.62			
Nov	9	1.60	Diarrhea still persists		
	12		Is weak		
	14	1.62	Found dead at 12 M		

TABLE 12—*Average Number of Hours per Day of Exposure and Days Elapsed Before the Death of the Monkeys*

	Diet	Season	Exposure, Total Hours	Days of Restriction	Exposure, Hours per Day
M I	Corn oil	March 21–May 21	28.00	61.0	0.46
M II	Corn oil	March 20–June 6	24.50	76.0	0.32
Average for spring				68.5	0.39
M III	Corn meal	May 9–June 27	21.25	49.0	0.43
M IV	Corn meal	May 5–June 28	21.25	54.0	0.39
M V	Corn meal	May 9–June 30	22.75	52.0	0.44
Average for summer				52.0	0.42
M VII	Raw carrots	May 23–Nov 14	1.75	174.0	0.01

was fed raw carrots instead of corn oil, corn meal or corn meal and sweet potatoes, which obviously may have had an influence in the prolongation of life.

It is of further interest to note the remarks as to the appearance of the skin and mucous membranes in connection with the amount of time of exposure to sunlight (monkeys M I and M II).

Finally, the authors' note of good condition followed by prompt signs of illness after further exposure is of especial interest M I, May 20 and 21, M III, June 26 and 27, M V, June 25, 26, 28 and 29

These notes suggest a critical influence of the short exposures following dietary restriction and previous exposure to sunlight*. In contrast, the animal fed raw carrots and given a minimum of exposure to sunlight (M VII) does not appear to have exhibited a sudden change in condition at any time. The significance of these comparisons could be determined only by further experiment under conditions controlled as to these factors

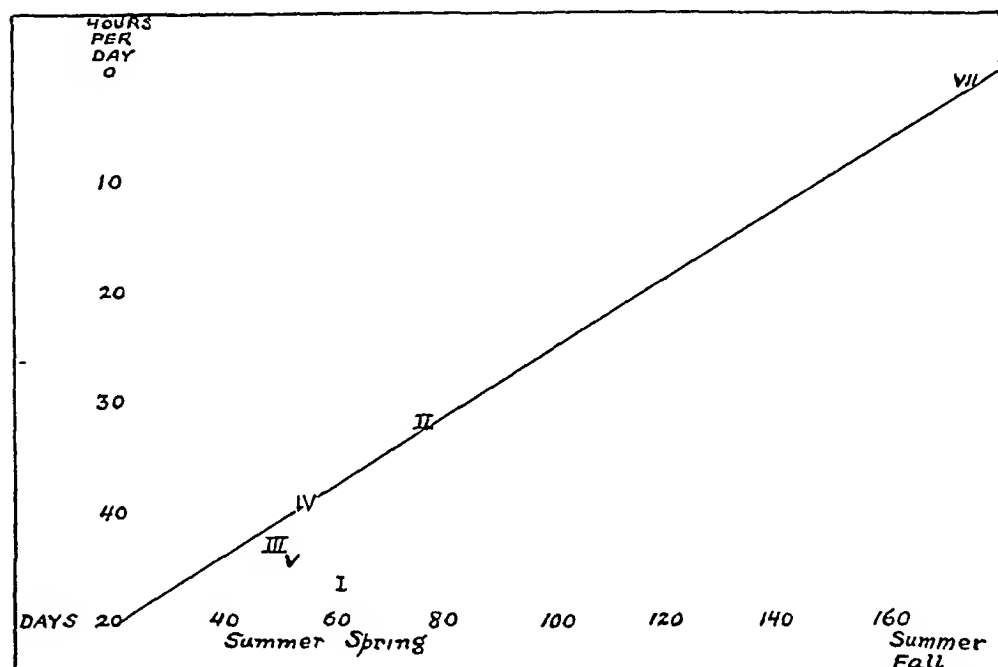


Chart 1—The hours of exposure to sunshine per day and the duration of life in days of monkeys I, II, III, IV, V and VII in Koch and Voegtlin's experiments in the study of chemical changes in the central nervous system as a result of restricted diet of vegetables

CREATINURIA AND THE AGE AND SEX INCIDENCE OF PELLAGRA

The relatively high incidence of pellagra in women, especially in those of the child-bearing period, suggests an examination of the metabolism of pregnancy for a possible bearing on the incidence of pellagra

During pregnancy certain marked changes in metabolism are normally found. If the mother is given an adequate diet, gains in the amount of nitrogen are easily made in the latter half of pregnancy,²⁹

* "That, indeed, exposure to intense light is capable of producing a localized hyperthermia of the central nervous organs has been borne out by the investigations of Hill and his co-workers" (Sundstroem reference 98)

not only ample for the growth of the fetus, but resulting in a gain to the mother. This was regarded by Hoffstrom and by Wilson as a reserve store of protein to provide for the needs of lactation. Hoffstrom and also Landsberg found, as well, large positive gains in sulphur (and in phosphorus, calcium and magnesium) (Haiding³⁹ and Macy and her associates⁶⁸). Values for creatinine are reported by several observers to be within normal limits. Cholesterol increases in the plasma throughout pregnancy. Ten days from delivery the changes characteristic of pregnancy have disappeared.

On the other hand, the urine is notably like that of the nonpregnant person under similar conditions, with the exception of the occurrence of creatine in the urine in the later stages of gestation³⁹ and for some time after. Such a finding has not been described in pellagra nor as an effect of ultraviolet radiation, and there is no evidence to relate it to the cholesterinemia characteristic of pregnancy, pellagra and ultraviolet irradiation, other than might be suggested by the fact that creatinuria and cholesterinemia are characteristic of the menstrual period as well as of pregnancy.*

The origin of creatine is undetermined,⁴³ and therefore its appearance in the urine of women intermittently and in pregnancy is not understood. However, there are other conditions characterized by creatinuria not necessarily pathologic, which, altogether, constitute an interesting parallel between the condition and the incidence of pellagra.

Hunter⁴³ stated

While the urine of the adult male on a creatine-free diet contains no creatine, that substance is a normal and constant associate of creatinine in the urine of children of either sex up to the age of puberty.

MacLeod⁶⁷ stated

Creatine is present in the urine of children in considerable amount, but in that of adults only in traces. In the first years of life the creatine of boys' urine may amount to one-half the total creatine and creatinine, but it becomes gradually less and practically disappears at about seven years of age. Girls, on the other hand, continue to excrete creatine until about puberty, after which, although ordinarily absent, it reappears in the urine at each monthly sexual cycle, and is present during pregnancy and for some days after delivery. Feeding creatine to children causes it to appear in the urine, accompanied usually by a slight increase in the creatinine. The same results can be observed in women during the monthly periods, when as much as 0.1 Gm. may be present, and during pregnancy. Creatine is also present in the urine of most if not all mammalia. Fasting causes the creatine and creatinine metabolism of the adult to become like that of the juvenile metabolism.

Certain observers deny any special association of creatinuria with menstruation, though recognizing its intermittent occurrence in women (Hunter, reference 43).

Creatinuria may be induced or increased in both men and women by a great variety of experiments or pathologic conditions.⁴² The most important forms of induced creatinuria are those produced by starvation, deprivation of carbohydrate (including diabetes mellitus, pancreatic diabetes and poisoning by phlorhizin, hydrazine, epinephrine or sodium selenite), wasting diseases generally, exophthalmic goiter, muscular atrophies and dystrophies and perhaps acidosis. In muscular atrophies or dystrophies, 90 per cent or more of administered creatine, even in small doses, appears unchanged in the urine (Hunter,⁴¹ p 603). Fontali (quoted by Hunter,⁴³ p 605) found a marked creatinuria following total thyroidectomy in dogs.

Koch and Voegtlin⁵⁰ referred to another characteristic of juvenile metabolism. "During growth the relation of protein sulphur and neutral sulphur is changed to a striking degree," as is shown in table 13.

TABLE 13—*Comparison of Neutral Sulphur with Protein Sulphur in the Brain of the Albino Rat at Different Ages*

	Protein Sulphur*	Neutral Sulphur*
1 day	30.5	48.2
10 days	44.5	45.4
20 days	56.4	28.6
40 days	63.7	18.2
120 days	61.8	18.7
210 days	63.8	14.5

* The figures represent the percentage of the total sulphur.

"During the early stages, when growth is proceeding rapidly and chemical activities may be considered to be at their height, the proportion of noncolloidal, relatively smaller, neutral sulphur molecules is at a maximum. As the tissues grow and become more highly differentiated and mature, more and more protein is laid down as structural material, and the proportion is shifted in the direction of the protein sulphur." A comparison of the cortex of man at 2 years and at maturity illustrates this point.

	Protein Sulphur	Neutral Sulphur
2 years cortex	63	22
19 years cortex	73	12

The only conclusion permitted with reference to creatinuria is that it is indicative of some departure from the relatively fixed and stable metabolism of the normal adult male. "The avidity, if it may be so expressed, of the muscle for creatine and its efficiency as a machine develop together, and as they develop, creatine disappears from the urine" (Hunter,⁴² p 611). With regard to the sexual influence, Hunter stated "perhaps if the point were examined it would be found, as Stearns and Lewis seem to infer, that women leading a life of abundant

muscular activity exhibit no creatinuria at all" (p 612) The athletic girl tends to minimize the apparent influence of the gonads in the metabolism of sex

The available data appear to justify the statement that during the first years following intra-uterine life, with respect to creatinuria, the metabolism of both boys and girls resembles that of the mother The escape of the adolescent male from this characteristic seems to be attributable to a gonadal influence, habits of exercise, food and possibly exposure to solar radiation, or to a combination of these, with or without other factors Tonic doses of ultraviolet rays tend to establish the nitrogen equilibrium on a higher level, thus tending to "muscu-

TABLE 14—*Race and Sex of Reported Cases*

States	Reports		White		Colored		Race and Sex Not Reported	Total Cases	Deaths	Death Rate per 100 Reported Cases
	Cards Mailed	Replies	Male	Female	Male	Female				
Virginia	2,359	823	174	302	49	103		628	349	55.59
North Carolina	1,849	521	543	1,201	130	277	261	2,412	1,067	44.37
South Carolina	1,275	287	357	772	120	351	280	1,880	582	30.95
Georgia	3,022	735	985	2,142	166	575	690	4,558	1,582	34.70
Kentucky	3,601	723	159	283	15	24	32	513	220	42.88
Alabama	2,418	561	150	988	133	680	363	2,314	859	37.12
Mississippi	2,009	561	433	954	249	907	352	2,895	1,250	43.17
Louisiana	1,930	446	123	215	69	200	63	670	296	44.17
Total	18,463	4,657	2,924	6,857	931	3,117	2,041	15,870	6,205	39.1*
Colored			931	3,117						
			3,855	9,974						
							White		Colored	
Male							2,924		931	
Female							6,857		3,117	
							9,781		4,048	

* Aggregate fatality rate per hundred reported cases

larity", a normal diet is a necessary basis for this effect The influence of food, work and light is almost inseparably bound up under ordinary living conditions

It may also be noted that the tendency to creatinuria and the incidence of pellagra are inversely correlated with the functional capacity for the growth of hair as seen in beardless youth, bearded manhood and bald old age

Possibly the tendency to creatinuria may be bound up with the fluctuations in metabolism characteristic of the menstrual cycle and pregnancy in women The basal metabolic rate of both boys and girls is relatively high, but is subject to a sharp decline not comparable with the gradual descent of any other decade The metabolic demands of growth are hardly constant or steady In relation to the degree of muscularity or "active protoplasmic tissue," these fluctuations may be of significance

The earlier data relative to race and sex incidence of pellagra in the United States are represented in table 14, from Lavinder⁵⁸

Bulletin 153 of the Hygienic Laboratory (table 15) gives the age and sex incidence found among the white population of the cotton-mill villages studied in 1917

The figures of Lavinder show an incidence of pellagra in the female as compared with the male of more than 2 to 1, but those of the cotton-mill villages studied show that this increased incidence in the female is limited to certain age groups. In table 15 there is a notable parallel incidence of pellagra, with reference to age and sex, and the tendency to creatinuria described, which suggests that a better

TABLE 15—*Incidence of Pellagra Among White Persons of Different Ages and Sexes in Twenty-Four South Carolina Cotton-Mill Villages During 1917*
(by Age Groups Arranged to Show the Greatest Age Variations for Both Sexes)

Age Group	Total			Male			Female		
	Pellagrins			Pellagrins			Pellagrins		
	Total Persons†	Number	Rate per 1,000	Total Persons†	Number	Rate per 1,000	Total Persons†	Number	Rate per 1,000
All ages	22,050	1,147	52.0	10,812	483	44.7	11,238	664	59.1
Under 2 years	1,130	3	2.7	500	2	3.6	570	1	1.8
2 to 4 years	2,141	165	77.1	1,124	89	79.2	1,017	76	74.8
5 to 9 years	3,105	367	118.2	1,574	193	122.6	1,531	174	113.7
10 to 14 years	2,605	226	86.7	1,329	131	98.6	1,276	95	74.5
15 to 19 years	2,722	21	7.7	1,212	4	3.3	1,510	17	11.3
20 to 39 years	6,998	234	33.4	3,355	10	3.0	3,643	224	61.5
40 to 49 years	1,669	69	41.3	841	17	20.2	828	52	62.8
50 to 59 years	954	36	37.7	403	18	38.9	491	18	36.7
60 years and over	726	26	35.8	354	19	53.6	372	7	18.8
20 years and over	10,347	365	35.3	5,013	64	12.8	5,334	301	56.4

* From Hygienic Laboratory Bulletin, no. 108

† As enumerated between May 1 and July 15, 1917

understanding of creatinuria might throw further light on the etiology of pellagra. If the suggestion of Harding and Young (quoted by Hunter,⁴³ p. 620), that creatine is a derivative of cystine, should be confirmed, a possible influence of an error in sulphur metabolism as a factor in the etiology or course of pellagra would receive some support. In this sense it may be noted

In the age group from 2 to 4, neither sexual characteristics nor habits of the two sexes have become sharply differentiated, and neither sex is much exposed to solar rays (male 79 female 74)

In the age group from 5 to 9, the same comparison holds approximately (122 113)

In the age group from 10 to 14, the secondary sex characteristics are not yet fully developed, but the male is distinctly more a denizen of the open spaces (98 74)

In the age group from 15 to 19 the menstrual function has been established in the female and apparently outbalances the influence of any climatic or other factor to which the male is exposed (3 11)

In the age group from 20 to 39, not only menstruation, but more especially pregnancy introduces profound recurring alterations in the metabolism of the female, and the incidence of pellagra assumes the ratio of 3 61. The genuineness of the influence of pregnancy seems to be borne out by a ratio in the married woman as compared to her single sister of 52 12 (Hygienic Laboratory Bulletin,⁴⁵ p 19)

In the age group from 40 to 49, as a disturbing influence on metabolism the menopause appears to rank with menstruation and pregnancy (female 40 to 49, 62 20 to 39, 61), and "the male equivalent of the menopause," or the slowing down of the metabolic rate, is represented by an increased incidence of pellagra in this decade (male 40 to 49, 20 20 to 39 3, resulting in a ratio between the sexes for the age period of from 40 to 49 of, male 20 female 62)

In the age group from 50 to 59, as the menstrual cycle has ceased and the child-bearing period has passed, the relatively housed existence of the female again becomes apparent in its effects, and the ratio is 38 36. After 60 years, this set of circumstances is again represented, but in sharper contrast, by a ratio of 53 18.

The foregoing paragraphs, of necessity, are presented merely as suggestive, in view of the lack of any positive knowledge as to the premises.

GEOGRAPHIC DISTRIBUTION OF PELLAGRA IN RELATION TO ISOTHERMAL LINES

It has long been observed that pellagra is a disease chiefly of north temperate latitudes. Voegtlin's map (chart 2) clearly indicates this tendency. His statement¹¹² of the geographic distribution is on a historical basis and is as follows: It was first discovered in northern Spain. About twenty years later, its existence was recognized in northern Italy, then in the southwestern part of France, in the Balkans, especially Roumania, and more recently in lower Egypt, Mexico, the West Indies and the United States, appearing in endemic form in all of these countries. A few sporadic cases have been reported from Great Britain, Canada, South Africa and India.

Wood's¹²⁰ statement in his article revised by Taylor describes a similar but somewhat more extended distribution.

At the present time the countries chiefly afflicted with pellagra are Italy, Roumania, the United States, France, Spain, Egypt, Serbia, Austria. Its occurrence also in South Africa, the West Indies, Hungary, Russia, Macedonia, Bulgaria, Greece, Turkey, Algeria, Tunisia, Rhodesia, Central Africa, Asia Minor

Persia, India, the Straits Settlements, Hawaii, Mexico, Brazil, Colombia and Argentina is noted, and in most of these countries it offers a medical problem of more than academic interest. It is said to have occurred in New Caledonia, and possibly Central America. A few cases have been noted in Korea.

Table 16 shows the approximate latitude of the countries in which pellagra is endemic and also their relation to the isothermal lines of summer and winter. These lines are also shown graphically in chart 3 for the northern and southern hemispheres, respectively. Practically all areas of endemicity lie along the isothermal line of 80° F. in summer.



Chart 2—Geographical distribution of pellagra (After Voegtlin U. S. Pub. Health Rep. **35** 1436 [June 18] 1920)

(July, North, January, South), regardless of its latitudinal variations. It is also further noted that where areas of endemic pellagra occur along the line of 80° F. the isothermal belt between 40 and 50° F. winter temperature (January, North) closely approaches the curve of 80° F. for summer, and where this approximation does not occur, with minor exceptions, pellagra is not reported as endemic. The exceptions lie in the torrid zone and include southern India and the Straits Settlements in the eastern hemisphere, and Mexico, the West Indies and Hawaii in the western hemisphere.

With regard to the temperate zone, it would appear that as a result of a hot summer and a cold winter, either directly or through some influence associated with or arising out of this sequence of temperatures representing sharply contrasting seasons, pellagra tends to be endemic. With regard to the torrid zone, it is possible that the minor endemic areas of pellagra reported in this latitudinal belt are apparent rather than true exceptions to the general condition of sharply contrasting seasons. Though there is no considerable variation in the summer and winter temperatures, the land areas of southern Asia are

TABLE 16—*Geographic Distribution of Pellagra, Showing the Approximate Latitude and the Relation to Summer and Winter Isothermal Lines*

	Approximate Latitude, Degree	Average Summer Tempera- ture, F (July N) (Jan S)	Average Winter Tempera- ture, F (Jan N) (July S)
Italy, northern	45 N	70 80	40
Roumania	45 N	70 80	30
United States, southern	33 N	80	40 50
France, southwestern	43 N	70 80	40 50
Spain, northern	43 N	70 80	40 50
Egypt, lower	30 N	80 90	50-60
Serbia	43 N	70 80	40
Austria, southern	47 N	70 80	30 40
South Africa	30 S	80 90	60 70
West Indies	20 N	80	70 80
Hungary	47 N	70 80	30 40
Russia, Georgia	42 N	80	40
Macedonia	40 N	80	40
Bulgaria	42 N	80	40
Greece	40 N	80	40 50
Turkey	40 N	80	50
Algeria	35 N	80 90	50 60
Tunisia	35 N	80 90	50 60
Rhodesia	20 S	80 90	70
Central Africa	10 S	80 90	80 90
Asia Minor	40 N	80	50
Persia	35 N	80 90	50 60
India, southern	10 N	80	80
Straits Settlements	0	80	80
Hawaii	20 N	70 80	70
Mexico, Yucatan	20 N	80	70
Brazil			
Colombia	5 N	80	70 80
Argentina	30 S	80	50 60

subject to the same seasonal reversal of currents of wind (monsoon winds) as occur in the waters of the Indian Ocean north of the equator, a southwest to northeast direction from April to October and a northeast to southwest direction from October to April. As a result, the eastern coast of southern India receives rain throughout October to April and the western coast from April to October. These conditions undoubtedly represent a seasonal variation in the amount of radiant energy received from the sun, though they are not associated with any conspicuous variation in temperature. The same considerations apply in large measure to Mexico, which, with India and the Guinea Coast of Africa represents the areas of land surface subject to a

steady wind from one direction for six months of the year and from the opposite direction for the other six months, with the result of sharply contrasting dry and wet seasons

The foregoing observations, though simple, present decided difficulties in interpretation. Obviously, solar rays, and probably certain features of variability in solar radiation, have an important bearing on the endemicity of pellagra. Is it a thermal influence or are the solar rays of ultraviolet wavelengths of greater significance? Which-ever wavelengths are important, is their importance attributable to

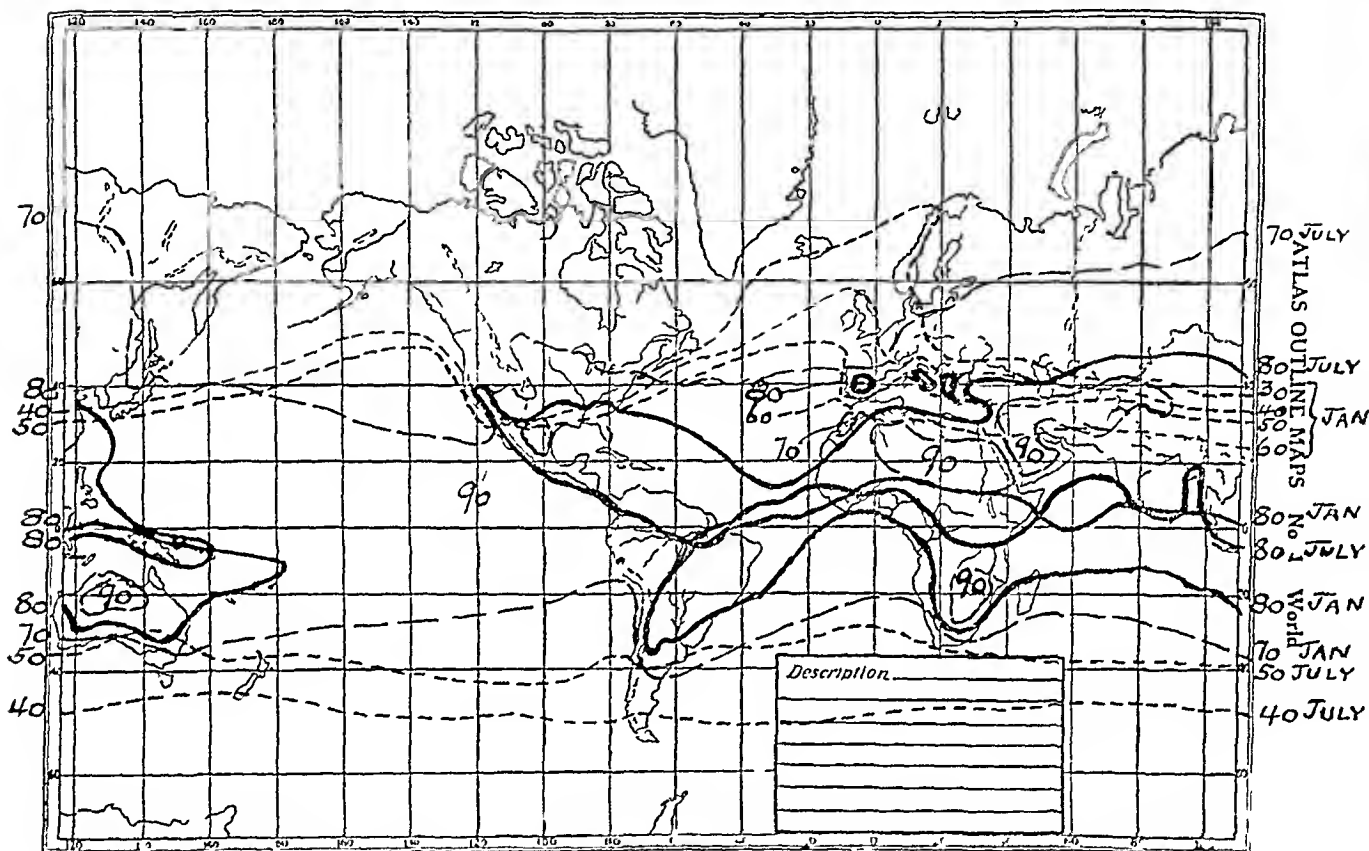


Chart 3—Isothermal lines. The heavy, unbroken line is 80 F summer (July, northern, January, southern), the average temperature. The long dash line is the same for 70 F. The continuous broken line enveloping numerals indicates an area of excess summer temperature, as 90. The short dash line with numerals indicates the average winter (January, northern, July, southern) temperature, as 50.

a direct effect on human metabolism or is it mediated through another influence such as plant culture? Is the climate referred to conducive to cultivation of certain crops and at the same time to the metabolic disturbances of pellagra, or does the cultivation of such crops result in exposure to solar rays of considerable intensity in summer as contrasted with low intensity in winter? Are these climatic features so

well adapted to certain crops that the population tends to pursue this particular form of agriculture to the exclusion of a more varied agriculture, resulting in a deficiency of a pellagra-preventive factor in the diet? Does the same intensive pursuit of one "money" crop (neither food for man nor feed for animals) result in an economic dependency of the population on this crop and economic depression under unfavorable market conditions? Does the consumption of one article of food as a large part of the staple diet render the population liable to a toxic or bacterial influence which the article of food may acquire under unfavorable conditions of harvesting, preparation or storage? These and doubtless other questions are involved in the observed geographic distribution of pellagra, and further data, or at least further analyses of data, are necessary for a solution of the problem. As before stated, this article attempts only to present some of the data at hand in a suggestive way.

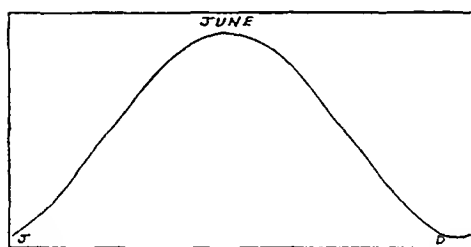


Chart 4—Curve of the angle of the sun in the northern hemisphere

CERTAIN FEATURES OF THE PHYSICS OF SOLAR RADIATION

The angle at which the sun's rays reach the earth is subject to diurnal and to seasonal variations. With regard to the former, suffice it to say that the maximum is at the sun's zenith, noon. The seasonal variation in the temperate zone is represented by a regular curve, with only one ascent to the maximum and one descent to the minimum during the year (chart 4). At the equator, twice a year, at the equinoxes, the sun's rays reach the earth at 90° . The minimum seasonal angle (winter solstice) for any latitude south of the arctic circle is determined by subtracting the latitude from $66^\circ 30'$. To this result the addition of 47° (the measure of the earth's surface between the tropics) gives the maximum seasonal angle of the sun for the latitude (summer solstice) (chart 5). The curve representing the sun's maximum angle throughout the year closely corresponds to the curve of mean temperature as observed in Virginia (chart 6) and also, except for the fall season, to the actual sunshine as recorded by a thermometric recorder (chart 129).

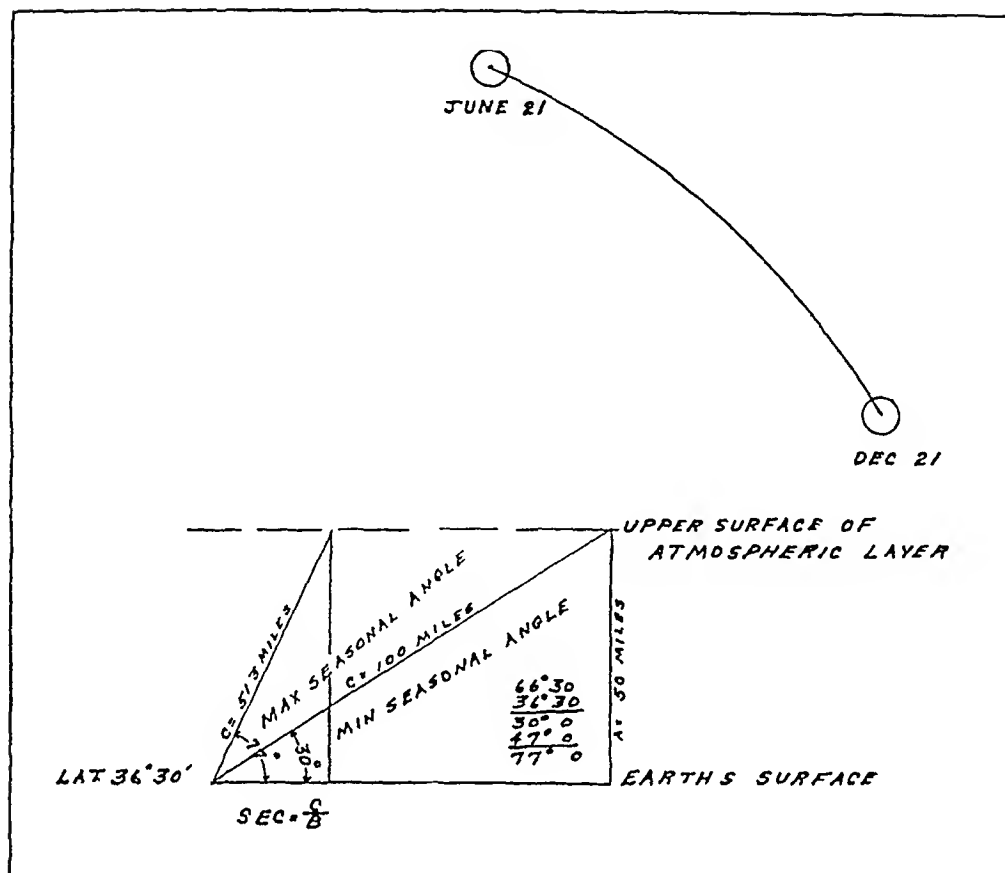


Chart 5—Trigonometry of the air mass or length of atmospheric penetration by solar rays at latitude $36^{\circ} 30' \text{ N}$

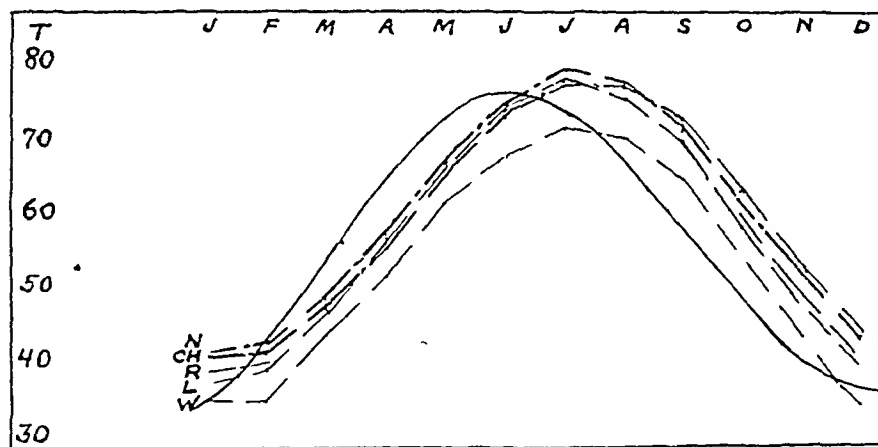


Chart 6—Virginia Curve of the angle of the sun The dash dot dash line indicates the average mean temperature The curve CH is for Cape Henry, N, Norfolk, R, Richmond, L, Lynchburg, and W, Wytheville

However, in the consideration of the influence of solar rays on biologic phenomena it would seem that the atmospheric belt surrounding the earth, through which the sun's rays filter, when taken into account in connection with a varying angle of the sun, might yield values to which certain biologic phenomena would be found to correspond. If the atmospheric belt is assumed to be 50 miles in thickness, then, given the angle of the sun, the length of the hypotenuse of the triangle may be readily calculated trigonometrically by means of the sine or cosecant of the angle (charts 5 and 7). No allowance has been made for refraction of the solar rays by the earth's atmosphere or for the curvature and irregularities of the earth's surface.

If this value is plotted out for all the angles between the seasonal minimum and maximum sun's angle for latitude 33° , the curve shown

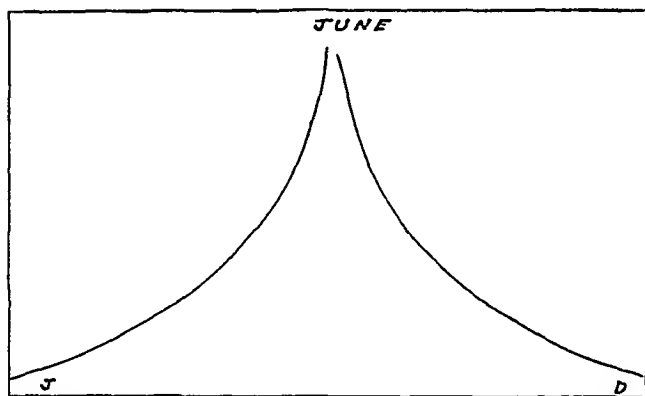


Chart 7—Curve of the air mass or length of atmospheric penetration by solar rays at about latitude 37° N

in chart 10 is obtained. Charts 8 to 12 show how materially the length of the solar rays' path through the earth's atmosphere is influenced by latitude.*

Considerable data have been collected on the influence of this factor of the air mass or the length of the path through the air (which hereafter will be referred to as air filter) on the intensity of solar radiation and its depletion by water vapor and by smoke and dust. (Kimball⁵⁰ and Kimball⁵¹) The ultraviolet is most sensitive to the depleting influences of the atmospheric filter⁵¹. Sunlight at sea level contains from 1 to 2 per cent ultraviolet, from 43 to 53 per cent visible and from 57 to 43 per cent infra-red. Sunlight on Mount Wilson contains from 2 to 5 per cent ultraviolet, from 50 to 55 per cent visible and

* The physiologic effect of ultraviolet rays is modified by the obliquity of incidence on the surface of the body (Stewart, reference 92). The mathematical implications are the same as those applicable to the air mass penetrated by the rays.

from 48 to 40 per cent infra-red, and on Mount Whitney, from 3 to 6 per cent ultraviolet, from 54 to 55 per cent visible and from 43 to 39 per cent infra-red

At Washington, D C (latitude, $38^{\circ} 56' N$, altitude 157 meters), with average atmospheric transmissibility, but little radiation of wave-

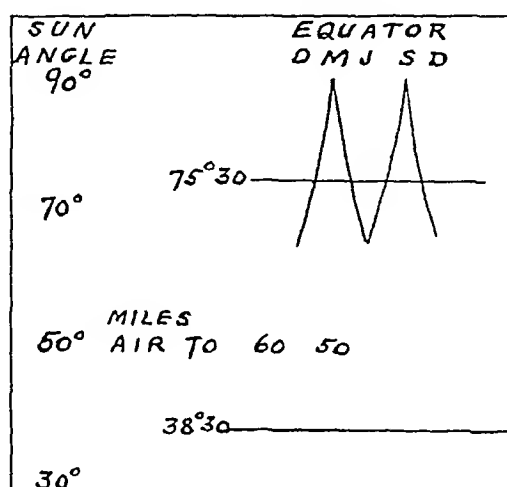


Chart 8—Annual curve of the path of the solar rays through the earth's atmosphere at the equator. The upper curve shows the sun's angle at the summer solstice at the upper border of the pellagra belt in the United States, the lower curve, the sun's angle at the winter solstice at the lower border of the pellagra belt in the United States.

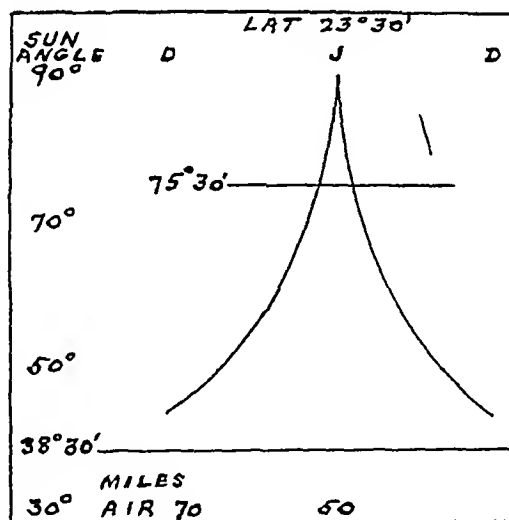


Chart 9—Annual curve of the path of the solar rays through the earth's atmosphere at latitude $23^{\circ} 30'$. The upper curve indicates the sun's angle at the summer solstice and the lower curve the winter solstice at the upper and lower borders of the pellagra belt in the United States.

lengths less than $350 m\mu$ penetrates to the earth's surface. On exceptionally clear days in winter, however, the receipt of this short wave radiation nearly equals that at Calama, Chile (latitude, $22^{\circ} 28' S$,

altitude, 2,250 meters), with average conditions of the sky, provided the comparison is made with the sun at equal zenith distances at the two stations ⁵¹ It appears that the ultraviolet radiant energy in sunlight

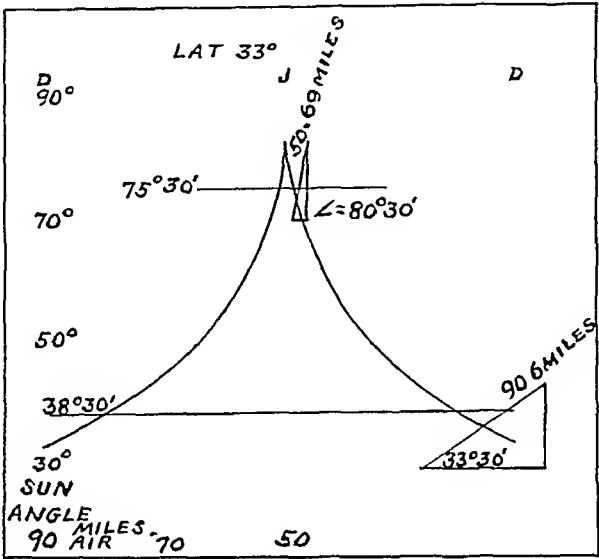


Chart 10—Annual curve of the path of the solar rays through the earth's atmosphere at latitude 33°. The upper curve indicates the sun's angle at the summer solstice and the lower curve the winter solstice at the upper and lower borders of the pellagra belt in the United States. The triangles show the calculation of the path at the maximum and minimum angles of the sun.

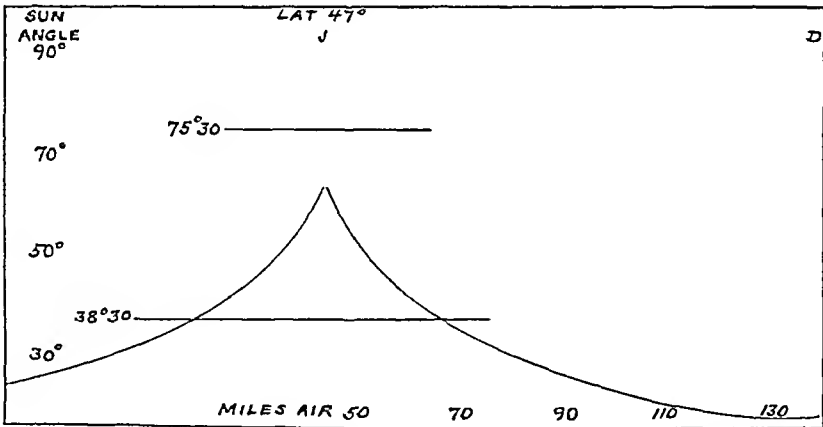


Chart 11—Annual curve of the path of the solar rays through the earth's atmosphere at latitude 47°. The upper curve indicates the sun's angle at the summer solstice and the lower curve the winter solstice at the upper and lower borders of the pellagra belt in the United States.

increases rapidly with an altitude above sea level and is diminished markedly by water vapor in the lower atmospheric layers. The distribution of the water vapor content of the atmosphere is such that, in general,

at sea level it tends to equalize the intensity of ultraviolet at different latitudes and at different seasons of the year ⁵¹

Kimball ⁵¹ gave the values shown in table 17 for wavelengths below $346\text{ m}\mu$, indicating the actual and relative influence of air mass and water vapor, with corrections for average dustiness

In table 17, the numeral 1 in line *iii* represents the air mass with the sun in the zenith, the numeral 2 the sun 60° distant from the zenith (angle 30°) The numerals in line *iv* represent water vapor measured in terms of depth of water that would be obtained if all the water vapor in the atmosphere were precipitated The greatly increased filtering power of smoke and dust of cities is suggested by the ratio of pyrhelimetric measurements on the campus of the University of Chicago and at Madison, Wis, only $1^\circ 18'$ farther north Taking the

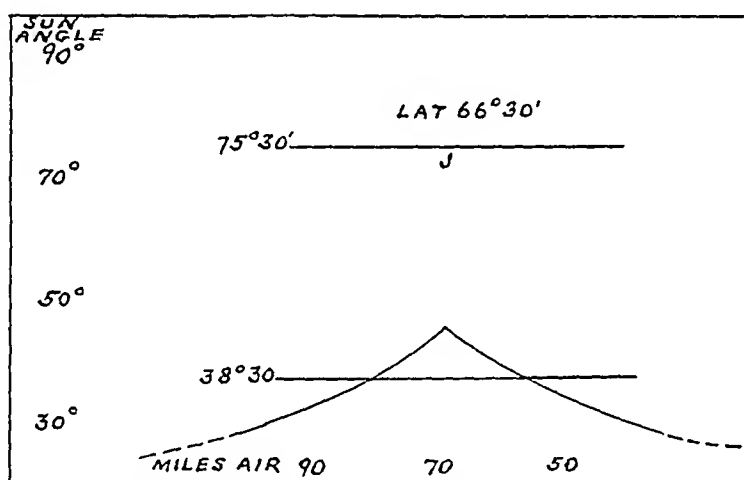


Chart 12—Annual curve of the path of the solar rays through the earth's atmosphere at latitude $66^\circ 30'$ The upper curve indicates the sun's angle at the summer solstice and the lower curve the winter solstice at the upper and lower borders of the pellagra belt in the United States

observations at Madison at 100, those at the University of Chicago from December to February were only 55 per cent, and in June, July and August, 84 per cent

In many tropical towns in the British and Dutch Indies near the coast in low-lying country with high humidity and much dust, the maximum intensity (of solar radiation) is not as great as that experienced in June at midday on the coast of the North Sea ⁵⁷

With regard to the relative influence of dry air and water vapor in depleting the ultraviolet rays of sunlight, while atmospheric pressure alters the value, with the sun in the zenith at sea level, radiant energy below wavelength $346\text{ m}\mu$ is only 38 per cent as intense as it was before entering the atmosphere, under the same conditions the presence

of water vapor in the amount of $w = 4$ cm (table 17) results in a depletion to 31 per cent of the value under depletion by dry air alone⁵¹

At Davos, Switzerland, Dorno observed the average midday intensity of solar heat, brightness and ultraviolet radiation by means of photo-electric cells (chart 13) (Clark,¹⁵ p 296) His curves not only show a midday variation for ultraviolet rays of much greater range than for heat or brightness, but that while heat and brightness* correspond to the curve of the angle of the sun (chart 4), ultraviolet intensity corresponds quite closely to the curve of the air filter (chart 7) This appears to be another demonstration of the influence of increased atmospheric mass to deplete the intensity of ultraviolet radiation and suggests that the depletion bears a direct relation to the length of the solar rays' path through the atmosphere

TABLE 17—*Values for Wavelengths Below 346 M μ*

Energy distribution in the solar spectrum, milliwatts per cm ² (dust free air)								
m	0	0.764	0.764	0.764	1	1	1	1
w (cm)	0	0	0.420	1.280	0	0.5	2.0	4.0
Below 346	4.2	2.3	2.1	1.6	1.6	1.4	1.0	0.5
Below 346		Corrected for average dustiness						
		2.2	2.0	1.6	1.4	1.3	0.9	0.4
		(Dust free air)						
m	2	2	2	4	4	4		
w (cm)	0.5	2.0	4.0	0.5	2.0	4.0		
Below 346	0.6	0.2	0.03	0.12	0.06			
Below 346		Corrected for average dustiness						
	0.5	0.2	0.02	0.08	0.06			

Laurens⁵⁷ said that

The importance of sky radiation is very generally ignored. It is evident that the beneficial effects of sunlight are in great measure due to its luminous and infra-red portions, as Rollier, Dorno and others hold. Dorno shows that sky radiations at Davos contain, in contrast to the rest of the spectrum, from two to four times more ultraviolet shorter than 366 m μ than does direct sunlight.

Abbott also demonstrated that on Mt. Wilson skylight was several times richer in violet and ultraviolet than was direct sunlight, while Tisdall and Brown find that December skylight in Toronto has an antirachitic effect almost as marked as that obtained by exposure to the available sunlight.

While areas of approximately the same latitude are subject to approximately the same filtration of solar rays so far as this is determined by air mass, when the observations are so controlled as to hold this factor constant, it is seen that the intensity of solar radiation at normal incidence may show different seasonal trends for areas not greatly separated in latitude. Because of a possible bearing on the geographic distribution of pellagra in Italy, this seasonal variation is

* Kimball (reference 50) showed curves for total radiation that correspond more closely to the length of the path of the solar rays than to the angle of the sun.

illustrated here by the reported observations at three Italian stations. The observations are based on different air masses for the different stations, but nevertheless a constant air mass throughout the year for a given station. They are based on pyrheliometric measurements of solar intensity rather than ultraviolet radiation, but the ratio of ultraviolet to the total probably does not vary greatly at the points mentioned. The stations, their altitudes and latitudes and the periods of observation are as follows:

Naples 149 meters, $40^{\circ} 32' N$, December, 1913, to January, 1915

Florence 73 meters, $43^{\circ} 46' N$, June, 1915, to December, 1917

Modena 51 meters, $44^{\circ} 39' N$, March to November, 1900, July to September, 1901, January, 1902, to June, 1903

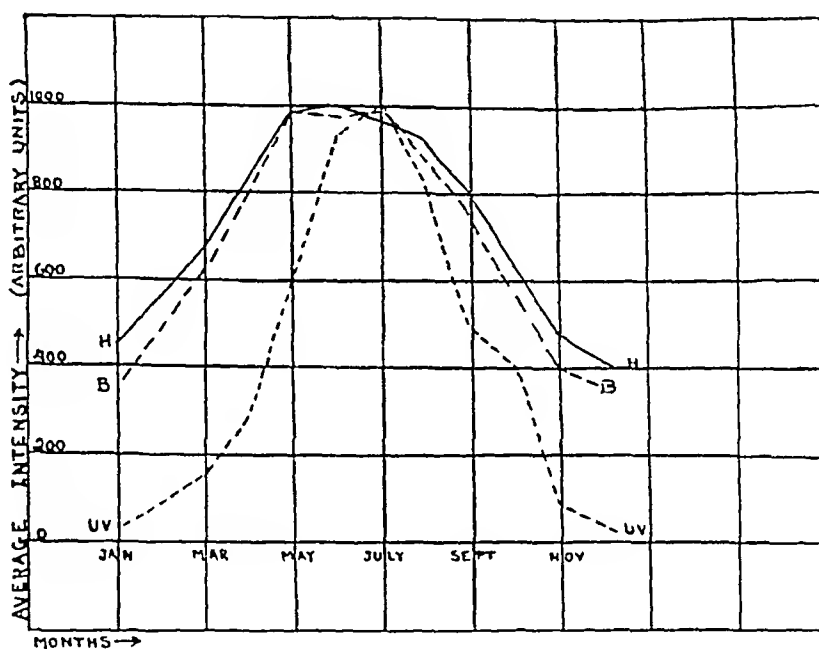


Chart 13—Average midday intensity of solar properties. The curve *H* indicates the heat, *UV*, ultraviolet radiation, *B*, brightness, throughout the year at Davos, Switzerland. (After Dorno, quoted by Clark, J. H. *The Physiological Action of Light*, *Physiol Rev* 2: 277, 1922.)

The latitudinal boundaries of Italy are approximately 47° and $37^{\circ} N$. A description of Christmas at Naples is suggestive of climatic conditions at the same season in Florida, 10° farther south. Reference to chart 14 reveals a maximum intensity of solar radiation in winter in Naples (for a given air mass), thus tending to offset the increasing directness of the sun's rays in summer, and a reversed condition with maximum in summer in Florence and Modena, only about 4° farther north, thus tending to accentuate the increasing directness of the sun's rays in summer. An especially sharp rise is noted in March at Florence and at Modena.

These measurements of solar intensity cannot be taken as measurements of solar light or heat received during any given period of time. Variability in the percentage of possible sunshine may occur directly with measurements of solar intensity or otherwise. This factor, in its application to the measurements at Washington, D C, and a comparison of pyrheliometric measurements at Mount Weather, Va, and Modena, Italy, are shown in table 18 (Kimball⁵⁰)

The average sunshine (percentage of possible) at Washington, D C, for the twenty-seven year period of observation prior to 1920¹⁰⁷ was as follows

Jan	Feb	March	April	May	June	July	Aug	Sept	Oct	Nov	Dec	Annual
47	54	55	58	61	62	64	61	64	61	55	49	58

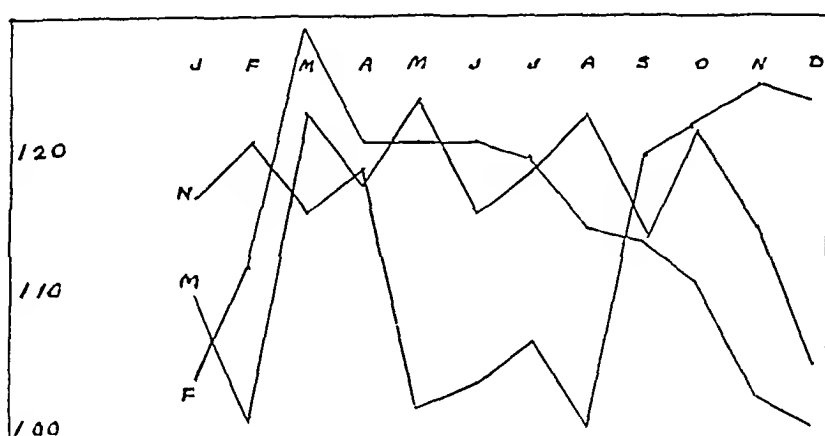


Chart 14—Curves of the monthly means of intensity of the solar radiation at three Italian stations. The air mass was constant for each station throughout the year, but was variable in selection for different stations. The curve *N* is for Naples, *M*, Modena, and *F*, Florence. (After Kimball)

The curves of ultraviolet radiation so far referred to deal with the physics of light as distinguished from biologic effects. There is evidence to show that the erythral effectiveness of ultraviolet rays of different lengths varies greatly⁵⁷. For present purposes, it is sufficient to recognize that the erythral effectiveness of ultraviolet solar rays in general is well established. With regard to another effect of these rays, the antirachitic effect, Tisdall and Brown¹⁰¹ have furnished experimental evidence of maximal diurnal and seasonal variations.

THE INFLUENCE OF SEASON AND LATITUDE ON METABOLISM

The evidence with regard to the effect of season and latitude on metabolism is conflicting and inconclusive. There are probably ample data in various laboratories to determine whether there is a seasonal

trend in the average basal metabolic rates of normal and abnormal persons in the different latitudes of the northern hemisphere

The Far North—While animals capable of entering on a poikilothermic state as in hibernation cannot be considered to represent conditions in the human subject, the known facts connected with the hibernation of animals suggest that in these animals the metabolism is lowest in winter. Hibernating animals sleep in the arctic night, and, save for certain nocturnal species, in general, animals sleep in the diurnal night.

During hibernation, hypoplasia of the anterior lobe of the hypophysis is found (Cushing, quoted by Wells¹¹⁶). Cannon and his associates¹³ considered the sympathico-adrenal mechanism the immediate agency in the restoration of the dormant animal to activity.

TABLE 18—*Measurements of Solar Intensity*

Washington, D C, altitude 127 meters, latitude 38° 56' N													
	Jan	Feb	March	April	May	June	July	Aug	Sept	Oct	Nov	Dec	
A2	1.22	1.17	1.14	1.07	0.99	0.89	0.91	0.95	1.04	1.11	1.17	1.22	
Mt Weather, Va, altitude 540 meters, latitude 39° 04' N													
	Jan	Feb	March	April	May	June	July	Aug	Sept	Oct	Nov	Dec	
A2	1.34	1.25	1.23	1.17	0.99	1.03	0.99	1.05	1.14	1.13	1.26	1.30	
Modena, Italy, altitude 51 meters, latitude 44° 39' N													
	Jan	Feb	March	April	May	June	July	Aug	Sept	Oct	Nov	Dec	
Am	1.10	1.01	1.23	1.18	1.24	1.16	1.19	1.23	1.14	1.22	1.15	1.05	
A2							1.01	0.95					

Bruman¹⁰ found a similar result after the use of atropine and considered the parasympathetic mechanism as predominantly responsible. It is possible that these observations may be consistent in view of the functional antagonism of the sympathetic and parasympathetic nervous systems and, further, that the influence of insulin and low blood sugar in bringing about an artificial state of hibernation and of injections of dextrose in terminating it²³ represents the mechanism of the sympathico-adrenal action in the natural process. Cannon and his co-workers¹³ found that the conditions that increase the adrenal secretion in lower animals likewise increase metabolism in man.

The observations of Lindhard on himself, which were made while he was living in Greenland, led him to the conclusion that his metabolism, like that of the hibernating animal, was lowest in winter. He attributed the increased metabolic activity of summer to light.

* The use of artificial radiation to offset the lack of solar radiation during the antarctic stay of the recent Byrd expedition probably precluded the collection of data relative to basal metabolism in the personnel of that expedition.

Laurens said that

Lindhard (Scandinavia) held that sunlight is the climatic factor which exercises the determining influence on respiration during the course of the year, the annual fluctuations in alveolar CO_2 tension being ascribed to the action of sunlight through an increase in the excitability of the center to CO_2 . Sunlight was also considered the determining factor giving mountain climate its special character

the consumption of oxygen and the production of carbon dioxide increased from midwinter to summer by 4 and 55 per cent, respectively. The changes were similar to those observed in Greenland and on mountain tops, and to those produced by the action of C arc irradiation

Briefly stated, the phenomena of hibernation include depression of metabolism, respiratory and pulse rates, respiratory quotient (McLeod,⁶⁷ p 584), body temperature, blood sugar content and the function of the endocrine organs, especially the hypophysis and the adrenals. The state of hibernation does not appear to be due directly to cold. Since the time of Lavoisier (quoted by Lusk⁶⁶), it has been recognized that cold increases the metabolism, and that in the hibernating animal a speedy transformation from the state of torpidity to one of activity occurs²² in case the surrounding temperature falls to a low level (Britton). If the metabolism is lowest in winter in northern latitudes, it is apparently due to causes other than cold alone.[†]

The Tropics—Generally speaking, the standards of normal metabolism have been derived from studies carried out in the upper levels of the north temperate zone. The reports are increasingly numerous to the effect that these standards are in excess of metabolic conditions normal to the lower levels of the north temperate zone and the zone of the tropics.¹⁴

With respect to temperature and sunlight, seasonal differences are least in the tropics (chart 8), and except for the possible influence of water vapor, seasonal variations in metabolism would be relatively improbable in the zone of the tropics.

Latitude of Boston and Chicago (42° N)—Gustafson and Benedict³⁶ reviewed the literature relating to seasonal variations of metabolism, and in a study of eight young women in one group and five in another, at Wellesley (Massachusetts, near Boston), they obtained

⁶⁷ Lusk (reference 66), quoting Lindhard and Hasselbalch and Lindhard, stated "The volume of respiration increases 26 per cent in summer. The intensity of the metabolic processes is not affected."

[†] Metabolism in the Far North may be lowest in winter without necessarily reaching its maximum in summer, the peaks possibly occurring in the fall and spring. Such an observation was recorded in one of Lindhard's subjects in 1912 (Scandinavia) (Laurens, reference 57).

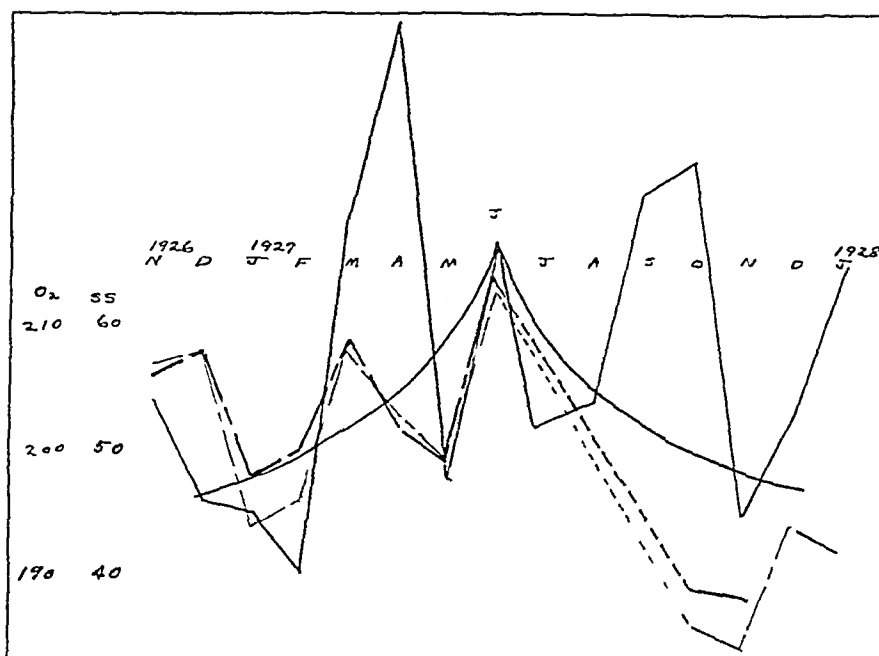


Chart 15—The continuous line in the curve is for the sunshine at Boston, from November, 1926, to January, 1928. The heavy broken line indicates the consumption of oxygen of eight subjects at Wellesley, the light broken line, the consumption of oxygen of five subjects at Wellesley. (After Gustafson and Benedict)

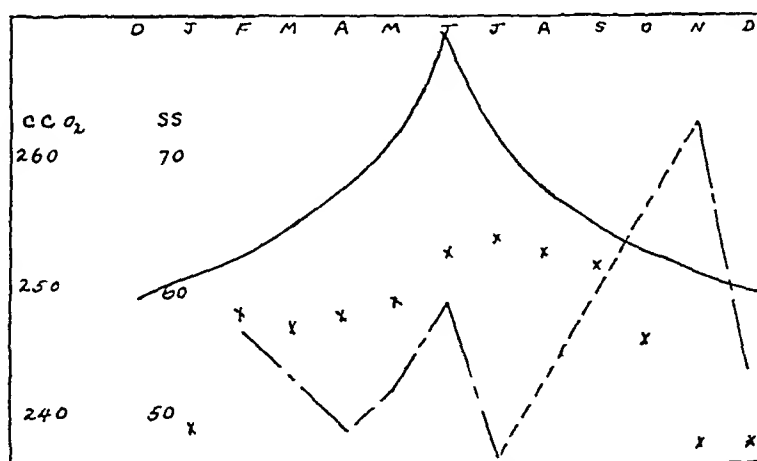


Chart 16—X indicates the average sunshine at Boston. The broken line indicates the consumption of oxygen of one subject observed at Boston over six and one-fourth years. (After Benedict and Carpenter)

similar curves for the two groups, the high peak of metabolism was found to be in June (chart 15) The variation was about 13 per cent

The male subject observed by Benedict and Carpenter⁵ over a period of six and a fourth years, at Boston, showed his highest rate in November (chart 16) The variation was about 10 per cent

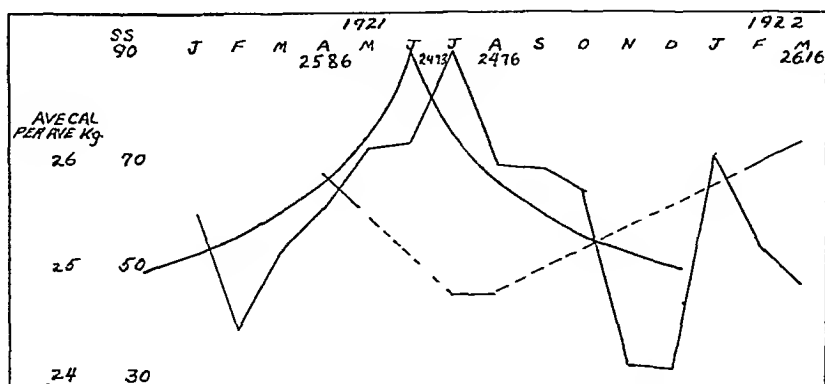


Chart 17—The continuous line indicates the sunshine at the University of Chicago, from January, 1921, to March, 1922, the broken line, the average calories per average kilogram of one subject observed at the University of Chicago (After Kunde)

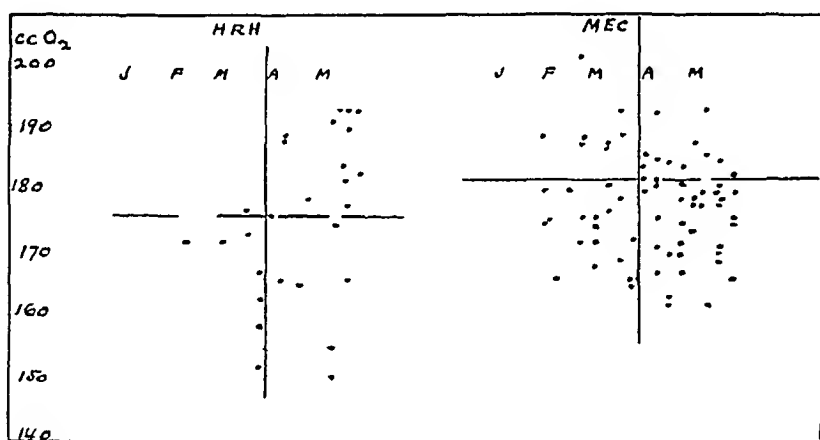


Chart 18—The fields of dispersion and trend of daily measurements of the consumption of oxygen of two subjects at New Orleans HRH indicates eighty observations, none between April 24 and May 7, MEC, ninety-six observations, none between February 10 and 18 (After Hafkesbring and Collett)

The female subject observed by Kunde⁵⁵ at the University of Chicago showed her highest rate in winter (chart 17) The variation was about 5 per cent

Thus, in this latitude the results reported by the several observers are not consistent, but taken as a whole they might be considered consistent as a latitudinal group if further investigation should show

a reversal between the seasonal peak in latitudes farther north and farther south, respectively, as the present data seem to suggest

Latitude of Southern United States—At New Orleans (30° N), Hafkesbring and Collett³⁷ observed a fall of about 5 per cent in the basal metabolism of two female subjects when there was a change

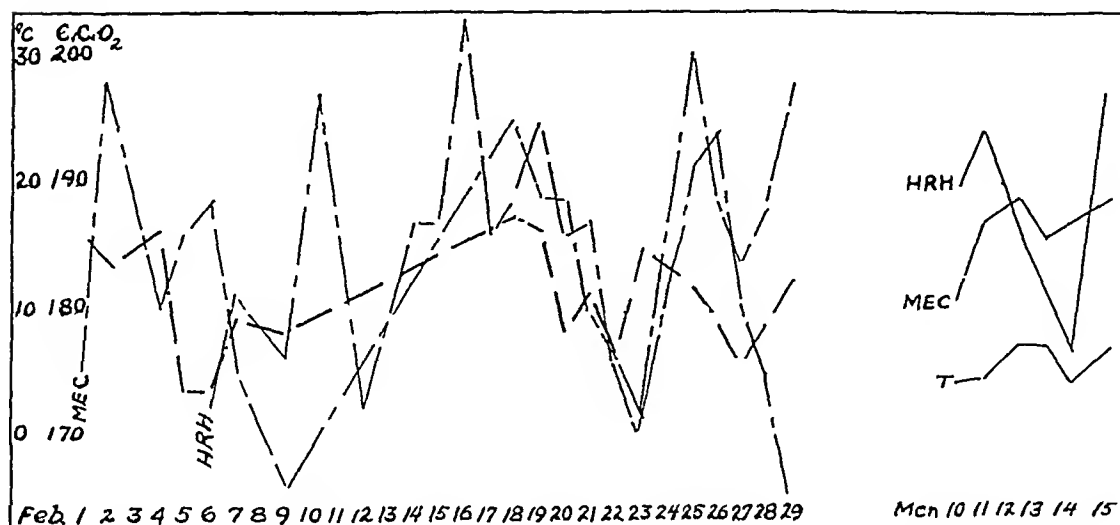


Chart 19—The dash, dot, dash line indicates the temperature at New Orleans in 1924. The long dash, short dash line indicates the consumption of oxygen of each of two subjects at New Orleans in 1924 (February). Curve T indicates the temperature, HRH and MEC, the consumption of oxygen in March, 1924. (After Hafkesbring and Collett.)

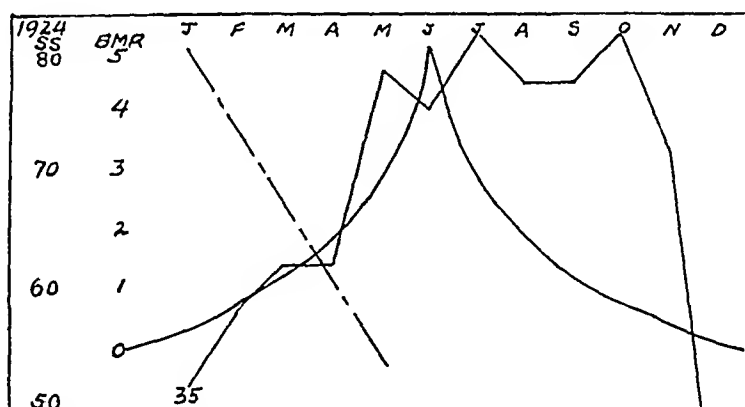


Chart 20—The continuous line indicates the cloud at New Orleans in 1924, the long dash, short dash line, the metabolic rate (decline) from "cold" weather to "hot" weather at New Orleans. (After Hafkesbring and Collett.)

from cold weather to hot weather. Chart 18 shows the trend and the fields of dispersion. Whether or not the observed fall from February to May was actually due to the increasing temperature of the air is open to question. Day by day in February the conspicuous tendency in both subjects was for the metabolism to rise and fall with a rise

and fall of the temperature of the air (chart 19) Somewhat the same diurnal trend is shown in March While a comparison by months shows a fall of metabolism with a rise of temperature (charts 18, 19 and 20), there are other climatic factors, including an increased percentage of sunshine and an increased angle of incidence of the sun's rays (a decreased air filter), that possibly should be considered as bearing on the fall in metabolism from February to May *

A lowered intake of protein with an increasing temperature would appear to be a probable factor in the seasonal decline and in the generally lower rates found in warm climates In certain sections of the population, this factor may be exaggerated by economic conditions, as described by Goldberger and his associates On the other hand, given even a moderate intake of protein, its specific dynamic action is definitely enhanced at temperatures prevailing during the summer in the south (Lusk,⁶⁶ p. 234)

Rubner said that

One hundred grams of meat did not change the metabolism at 20°, 25° or 30°, 200 grams of meat had no effect at 20° or at 7°, but at 25° and 30° there was an increase, although the food contained fewer calories than the requirement With 320 grams of meat there was a great increase above the starvation requirement, except at 7°, where it is a maintenance diet and the metabolism remains unchanged In other words, at a temperature of 30° the specific dynamic action of this amount of protein is capable of increasing the heat production above that of starvation by about 53 per cent, while at 7° there is no change whatever It is also evident that at a high temperature even a small amount of protein, such as 200 grams of meat, causes a considerable rise of metabolism

The suggestion that basal metabolism may be influenced by the solar rays appears to receive some support from the observations in

* Comparisons of this kind cannot be made without a consideration of the extent of exposure of the subjects to the prevailing external atmospheric conditions and the relative influence of these external conditions as compared with the influence of the indoor conditions at the time of the observation

The metabolism determined inside the house and that determined in the open, lying naked on the sand, usually show an increase for the latter, depending, it seems, on chemical regulation of the loss of the heat The increase is observed when the sun is not shining, as well as when it is, but always occurs when there is a wind so that it is most probably due to stimulation of the skin (Laurens, reference 57)

Kestner and his co-workers found that the sun at the seashore (and quartz mercury and carbon arc lamp radiation) strongly and immediately increases gaseous metabolism by its action on the skin, though the increase is diminished if there is a simultaneous heating effect, which brings the chemical heat-regulating mechanism into action The effect is specific, being called forth by a stimulus to the skin These observers reported that the basal metabolism was increased at high altitude in winter, but not in summer, and although it also occurred in the absence of sunlight it was much greater when the hands and face were exposed to the sun

Virginia They are limited and are open to the criticism that the determinations of metabolism were not made on subjects selected as normal The latter criticism is less valid as against the ultimate purpose in view, the demonstration of a reversed correlation between the average basal metabolism of subnormal persons on the one hand and the intensity of solar rays on the other hand, with special reference to the etiology of pellagra

It has been brought out that the filtering of ultraviolet rays varies with the curve of the air mass and with the amount of water vapor in the atmosphere It follows that these rays are of greater intensity at the summer solstice, with a minimum of water vapor With reference to the air mass filter, Dr P S Smith, in a personal communication, reported that for 1928 the average basal metabolic rates* (272) taken in the clinic at Abingdon, Va (latitude, 37° N), reached a low level in June Examination of his curve (chart 21) shows that the general trend is directly with the seasonal decreasing and increasing air filter Further, as to water vapor,† it is seen that after the summer solstice the curve of the average metabolic rate tends to be deflected upward and downward away from the curve of the air filter to correspond with a rise or fall in cloudiness In other words, the curve of metabolism varies inversely with the intensity of solar radiation

At Richmond, Va (latitude, 37° 32'), the same trends are noted The combined determinations of metabolic rate (1,976) for the years 1926, 1927 and 1928 are shown in chart 22 The rise in August to correspond with the rise in cloudiness is noticeable Since August is quite consistently a cloudy month in this geographic area, it is interesting to note a consistent rise in the metabolic rate, which was higher than in either July or September, in each year of the three years Reference to the relative low level of the average metabolism reached in the several years will be deferred until reference is made to the influence of a relatively cloudy winter season

From studies made on white men, chiefly physicians, and on Negro laborers in Brazil (Rio de Janeiro, latitude, 22° 54' S), Almeida (quoted by Dubois²²) suggested that in sufficient time all of the factors that modify the total metabolism will finally alter the value of the basal metabolism According to Almeida, the basal metabolism depends on all the factors which in passing have modified the intensity of the habitual metabolism Among these are muscular work, the level of the

* All rates above plus 20 being omitted so as to exclude definite hyperthyroidism

† For the present, reference to relative humidity was omitted, and only cloudiness was considered as it was observed at the nearest United States Weather Bureau station, Wytheville, Va , sixty miles distant

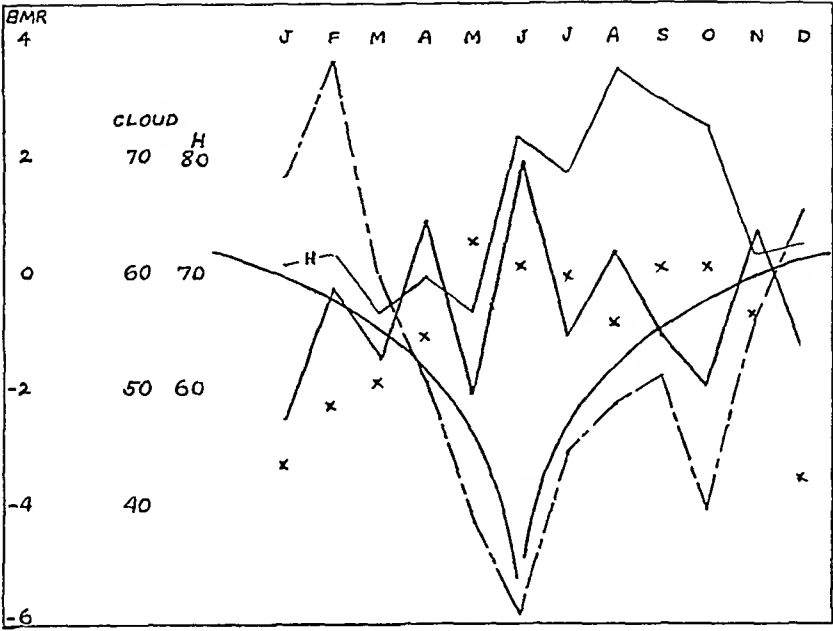


Chart 21—Southwest Virginia X indicates the average sunshine at Wytheville, the two continuous curve lines, the curve of atmospheric filter, reversed, curve *H*, the humidity at Wytheville in 1928, the continuous lines, cloudiness at Wytheville in 1928, and the broken line, the average basal metabolic rates at Abingdon, monthly, in 1928 (total determinations, 272)

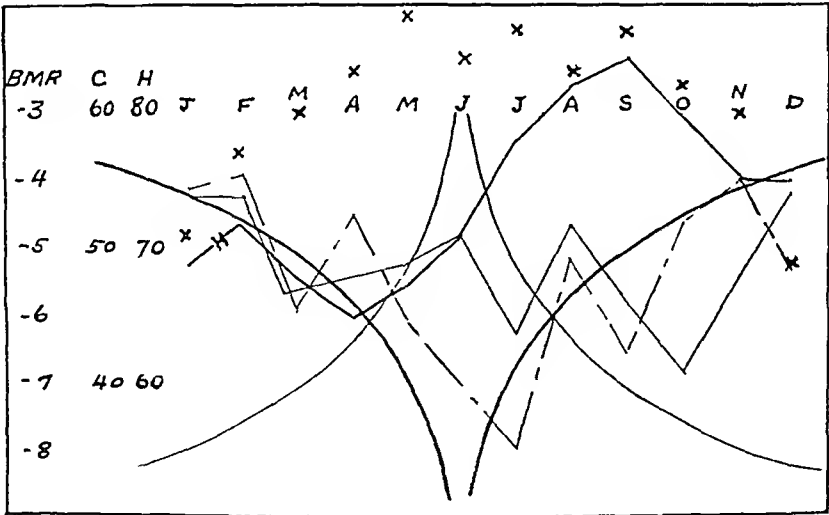


Chart 22—X indicates the average sunshine at Richmond, the continuous curves, the curve of atmospheric filter, curve *H*, the average humidity at Richmond in 1926, 1927 and 1928, the continuous line, the average cloudiness at Richmond in 1926, 1927 and 1928, and the broken line, the average basal metabolic rates at Richmond, monthly in 1926, 1927 and 1928 (total determinations, 1,976)

intake of food and the difference between the temperature of the body and the temperature of the air multiplied by the surface area. In the tropics, all of these levels are lower than those in the temperate zone. These ideas lead readily to the consideration of a hereditary level of metabolism or a genetic factor affecting the habitual rate.

The cotton-mill worker is the lineal descendant, and often merely the transplanted self, of the rural laborer of the southern part of the United States.

There has been recent experimental evidence to show that under certain circumstances rats may acquire and transmit to their progeny a capacity for growth and maintenance of nutrition devoid of vitamin B⁵⁴. In contrast to this adaptation, it would not seem contrary to biologic phenomena generally if a nutritive lack and a resulting metabolic depression were handed down from one generation to another. Such a feature seems to be exemplified in the epidemiology of endemic goiter.

If, as Almeida supposes, in sufficient time all of the factors that modify the total metabolism and in passing have modified the habitual metabolism will finally alter the value of the basal metabolism, it would appear that a perpetuation of factors tending to lower habitual and basal metabolism in the individuals of several generations would, in sufficient time, result in a level of metabolism which would constitute a characteristic that would tend to be passed on from one generation to another. Such a conception could well include a specific nutritive lack as tending to the development of pellagra. The characteristic in successive generations would not constitute an acquired character in the strict sense of persistence after the determining influences had ceased to operate, as the absence of the pellagra-preventive factor supposedly persists in the succeeding generations.

On this basis, possibly an explanation may be reached of the more recent observations that, contrary to earlier opinion, pellagra is not rare in children in the United States (Hygienic Laboratory Bulletin 153, p. 15). The children born of the first generation of pellagrous parents may well show an incidence of the disease differing from its incidence in children of countries such as Italy, where pellagra has been endemic for many generations and where the disease is considered to be rare in children under 15 years of age.

In view of the historic prevalence of pellagra in certain Mediterranean countries, including Italy, and the comparatively recent development of the disease in endemic form in the United States, it would be of interest to note whether immigrants coming directly from areas where the disease is endemic, for example, in northern Italy, to

the southern part of the United States exhibit a tendency to the development of pellagra more promptly than was shown by the peoples from northern Europe and equatorial Africa, by whom the southern states were settled and among whom pellagra did not appear in endemic form for several generations

Whether or not a different source of immigration might have resulted in an earlier appearance of pellagra in endemic form in the southern part of the United States, it hardly seems to conform to the data of the social and economic history of the South to suppose that food habits or food supplies in this area changed radically in the forty years elapsing from the time of the war between the states until 1907⁷⁸ On the other hand, the time estimated by Goldberger and his associates for the influence of a deficiency of food to become operative in the production of pellagra is in terms of weeks or months only Food, occupation and climatic factors do not appear to have undergone a sudden radical and pellagra-producing change

Under these circumstances it would seem necessary to assume the invasion of some infectious agent or the influence of some factor operating over a period of several generations with increasing intensity so as to result in the appearance of an endemic disease in 1907, which was hitherto unknown in this area except in sporadic form In view of the failure of well directed efforts to establish an infectious etiology, no other assumption seems to fulfil the conditions so well as the postulation of a genetic factor

Definition of Cloudiness—Though cloudiness and sunshine are in a real sense opposite values, according to the standards of the United States Weather Bureau, they are not exactly so Theoretically, 30 per cent of sunshine would be the equivalent of 70 per cent of cloudiness Actually, by the methods of the Bureau, they may be equivalent

The Bureau describes its methods of observation as follows "The following tables give sunshine for 148 stations (1914), the monthly amounts of sunshine and percentage of the possible as derived from the automatic records made by an instrument designated the 'thermometric recorder' illustrated in the preceding volumes of this series This instrument does not record satisfactorily the duration of sunshine for about one hour after sunrise and for about one hour before sunset, and on this account it has been considered necessary to apply to the record for these hours what has been designated a 'twilight correction' The amount of this correction is found by noting the comparative cloudiness of the sky during the time that elapses between the hour of sunrise and the moment the instrument begins to record and between the time the instrument ceases to act and the hour of sunset The average cloudiness of the whole sky is determined by numerous personal observations at all stations during the day time, and is given in the column 'Daylight' under cloudiness in the tables of Part III" (United States Weather Bureau Annual Report)

or they may vary as much as 15 per cent, as is illustrated by the month of December, 1921

	Sunshine	Theoretical Cloudiness	Actual Cloudiness	Variation
Wytheville, Va	34%	66%	66%	0
Charleston, S C	74%	26%	41%	15%

Therefore, while it is legitimate to reverse a vertical scale for cloudiness and present the largest figures at the bottom so that a rise in curves represents a relative increase in sunshine, the reversed scale for cloudiness cannot be used for an exact representation of sunshine

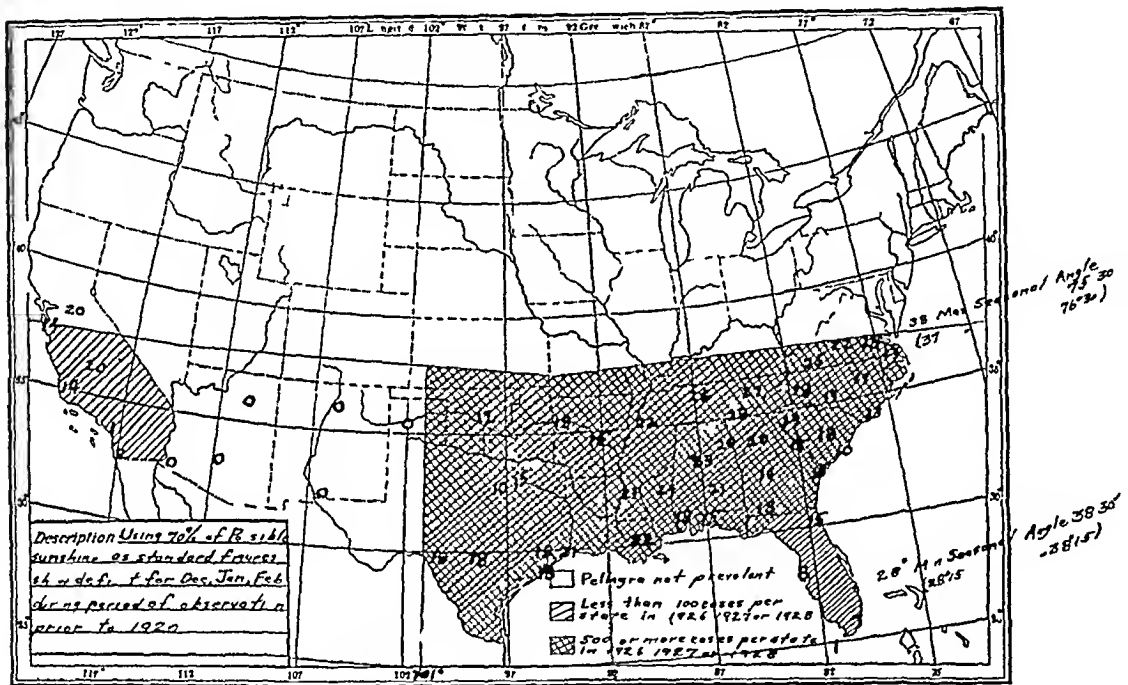


Chart 23—The shading represents the prevalence and distribution of pellagra in the southern United States in 1926, 1927 and 1928. The numerals indicate the deficit of sunshine for December, January and February, during the period of observation prior to 1920, 70 per cent of possible sunshine being used as a standard (From Bull W U S Weather Bureau)

ACCUSTOMED RADIANT ENERGY AND DEVIATION THEREFROM

The stationary population of any given area of the earth's surface is subject to deviation in at least three ways in the amount of radiation received from the sun: (1) variation in the altitude of the sun and the thickness of the air filter (annual regularity and seasonal variation), (2) variation in cloudiness (annual irregularity and seasonal irregularity) and (3) variation in exposure to the available sun in winter and to the inevitable sun in summer (annual irregularity and seasonal irregularity).

Laurens⁵⁷ found the metabolic effects of ultraviolet irradiation to be of greatest significance when taken into account with the accustomed exposure to these rays, and he concluded that probably any deviation from the usual, so far as radiant energy is concerned, acts as a stimulus that disturbs the metabolism of nitrogen, calcium and phosphorus

It is now proposed to examine certain features of pellagra as it occurs in the southern part of the United States with reference to the idea that, so far as radiant energy is concerned, there may be a critical maximum of exposure to solar rays beyond which a disturbance of metabolism conducive to pellagra results if the recent previous exposure has fallen below a critical minimum of safety (under certain abnormal conditions of nutrition), as a corollary, the least minus deviation of exposure to the available solar rays in winter and the least plus deviation of exposure to the inevitable solar rays in spring, summer and fall (within the parallels of latitude rendered critical by the earth's seasonal position in relation to the sun) probably tend to avoid such disturbances of metabolism as are conducive to pellagra.* Any difficulty arising from the involved construction of this paragraph may be somewhat relieved by recalling the principles underlying sunburn

The upper limit of the pellagra belt in the United States is defined approximately by latitude 38° N, at which the maximal seasonal angle of the sun is $75^{\circ} 30'$

For any given latitude the number of days the sun's angle is above or below a given degree at a given hour may be calculated, and the number of hours at which the angle is above or below a given degree may be calculated for any latitude at any season. Since the physiologic effect of irradiation is one of intensity multiplied by time (Warren, reference 115), both are to be taken into account. The element of time is involved in the amount of exposure as determined by occupation or other factors, as, for example, in the planting of cotton, and the element of intensity is involved in the fact that this crop is planted at or near the summer solstice. The tentative assumption is

Duration of elapsed time above a critical minimal angle is protective, duration of elapsed time below a certain minimal angle is sensitizing. Work in cotton-mills involves the principle of duration of time below the critical minimum.

If the zone of pellagra in the northern hemisphere is between latitude 38° and 30° , with a minimum seasonal angle of the sun of $28^{\circ} 30'$ to $36^{\circ} 30'$, and a maximum of $75^{\circ} 30'$ to $83^{\circ} 30'$, and if 34° is taken as the focal latitude and $36^{\circ} 30'$ as the protective minimum, the minimum for 34° is $32^{\circ} 30'$, 4° below the protective minimum, and since the sun travels 47° in 182.5 days, it is (at 34° latitude, with a minimum altitude of $32^{\circ} 30'$) below the protective minimum of $36^{\circ} 30'$ thirty-one days ($2 \times 4 = 8$ degrees) ($8 \div 47 \times 182.5$) in the year. At the upper latitude of 38° , a longer period elapses below the protective minimum, but the period above the critical maximum is not so great. If 50 miles is assumed to be the depth of the atmosphere, the difference in the atmospheric belt traveled by the sun's rays at an angle of $32^{\circ} 30'$ (latitude 34°) and $26^{\circ} 30'$ (latitude 40°), respectively, is 18.85 miles longer filter at latitude 40° (112.05 miles minus 93.2 miles), and the difference at $32^{\circ} 30'$ and $26^{\circ} 30'$ is 1.3 miles (52.1 minus 50.8).

The lower limit of the belt is defined approximately by latitude 28° N, at which the minimal seasonal angle of the sun is $38^{\circ} 30'$ (chart 23)

So far as the sun's angle is concerned, it would be inferred that solar rays have a pellagra-producing effect in areas receiving them at an angle of $75^{\circ} 30'$ or above, but in view of the relatively low prevalence of the disease in the tropics, a more efficient pellagra-preventive effect would be attributed to solar rays reaching the earth's surface at no time of the year below an angle of $38^{\circ} 30'$ * (Voegtlin's map, chart 2)

A pellagra-preventive influence ascribed to a minimal seasonal angle not falling below a critical point tends to be supported by the fact that, within the pellagra belt, if the sunshine of a given area is maintained at or above 70 per cent of the possible sunshine for the time of and following the winter solstice, December, January and February,† pellagra is not prevalent. By virtue of the absence of cloudiness, the solar rays received during the winter appear to have a protective influence of the same order as a minimal angle above the critical point, though this apparent protective influence of winter sunshine cannot be appraised without further consideration of relative densities of population (relatively sparse between longitudes 101° and 105° W) and the economic pursuits of the people. On the other hand, since in the United States the area apparently protected by a relatively high minimal angle of the sun in winter (Florida) is also relatively high in winter sunshine, confirmation of a supposed protection from a high minimal angle would have to be sought in areas farther south with a deficit of winter sunshine. However, the principle of protection by exposure to a total of solar rays not falling below a minimum does not seem to be involved in these distinctions

* The idea may be somewhat clearer if stated in terms of the adjacent side of the triangle rather than the angle itself or the hypotenuse. To those familiar with the folklore of the southern United States, the statement will be reminiscent of the rule concerning the ground-hog often quoted in connection with the second day of February.

† If one is accustomed not to cast a shadow of less than two and one-half times one's stride at noon during most of the winter and is rather accustomed (actually) to cast a shadow of one-half one's stride or less at noon during the summer (5' 1, or for a man 6 feet tall, 90 inches - 18 inches), one may not with impunity incur the deficiency of diet described by Goldberger.

‡ Possibly a shift of attention from the cloud of the three months December, January and February would reveal a sharper index than these three months. For example, the unusual cloudiness of February, 1927, throughout nearly the whole South appears to correlate better with the incidence of pellagra during that year as compared with the cloudiness of February, 1926, and the incidence of pellagra in that year (chart 24).

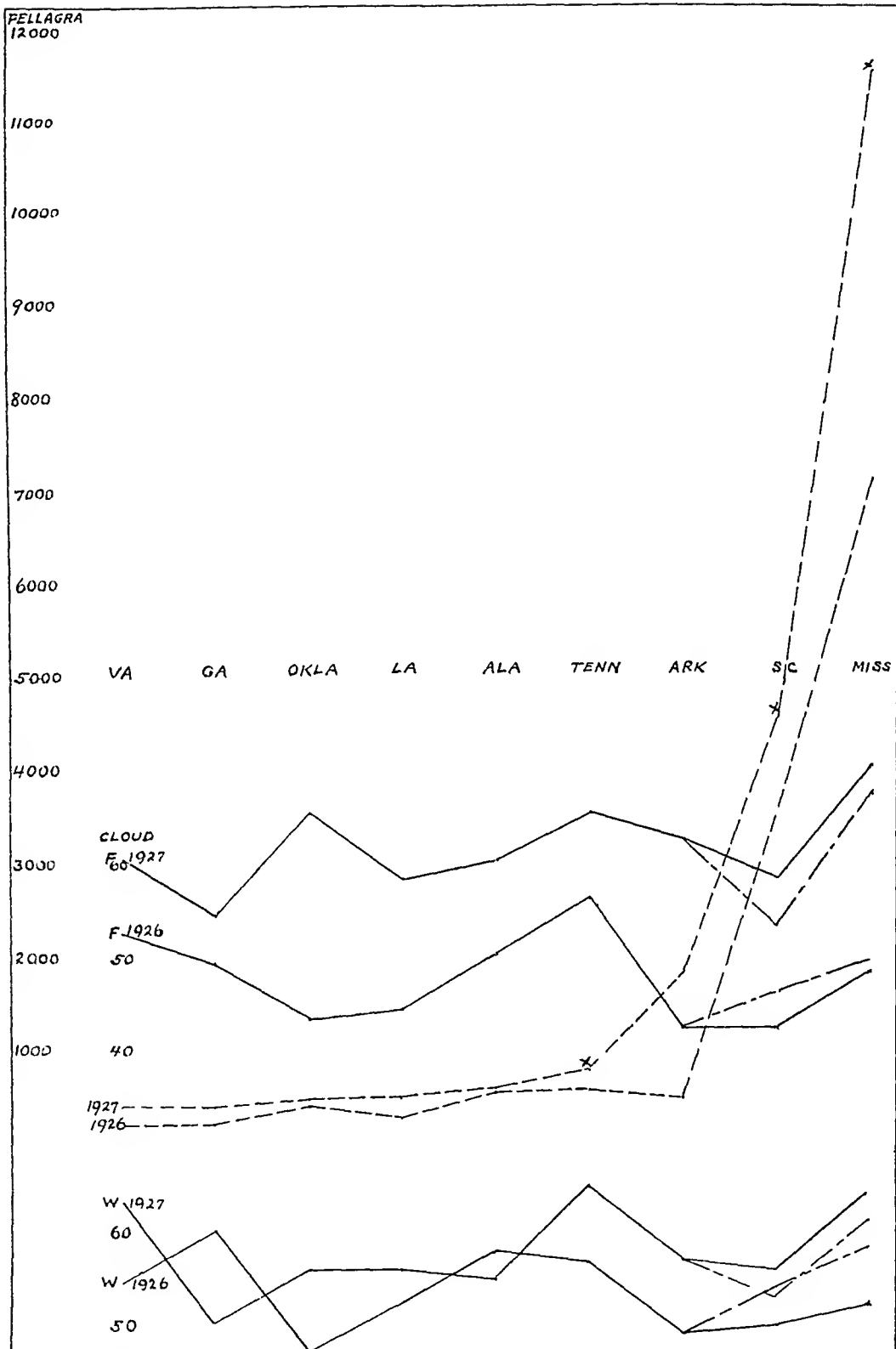


Chart 24—Nine states Curve *W* indicates the winter cloudiness for 1926 and 1927, using observations at all stations except for South Carolina, Greenville only, and for Mississippi, Memphis only, the continuous and broken curves *W*, same, using observations at all stations in each state The continuous broken line indicates the incidence of pellagra in 1926 and 1927 *F* indicates the February cloudiness for 1926 and 1927, using observations at all stations except for South Carolina and Mississippi, Greenville and Memphis only, the continuous and broken curves *F*, the same, using observations at all stations in each state

A sharp definition of the upper border of the pellagra belt in the United States seems to be supported by its distribution in the state of Virginia (chart 25) and Kentucky (chart 26) and a comparison of Arkansas and Oklahoma with Missouri and Kansas⁴

The sharp break in the pellagra belt shown at longitude 101° W is based on the reports of the distribution and prevalence of pellagra in Texas for the period from 1907 to 1911⁵⁸ (chart 27)

Examination of chart 23 shows that within the pellagra belt in the United States, in areas where there was no deficit of winter sunshine below 70 per cent of the possible sunshine (longitudes from 101° to 105° W), pellagra is not prevalent, that where there is a slight

OUTLINE MAP
STATE OF VIRGINIA
PUBLISHED BY
STATE HEALTH DEPARTMENT
PELLAGRA

X 1927
O 1928
□ 1929

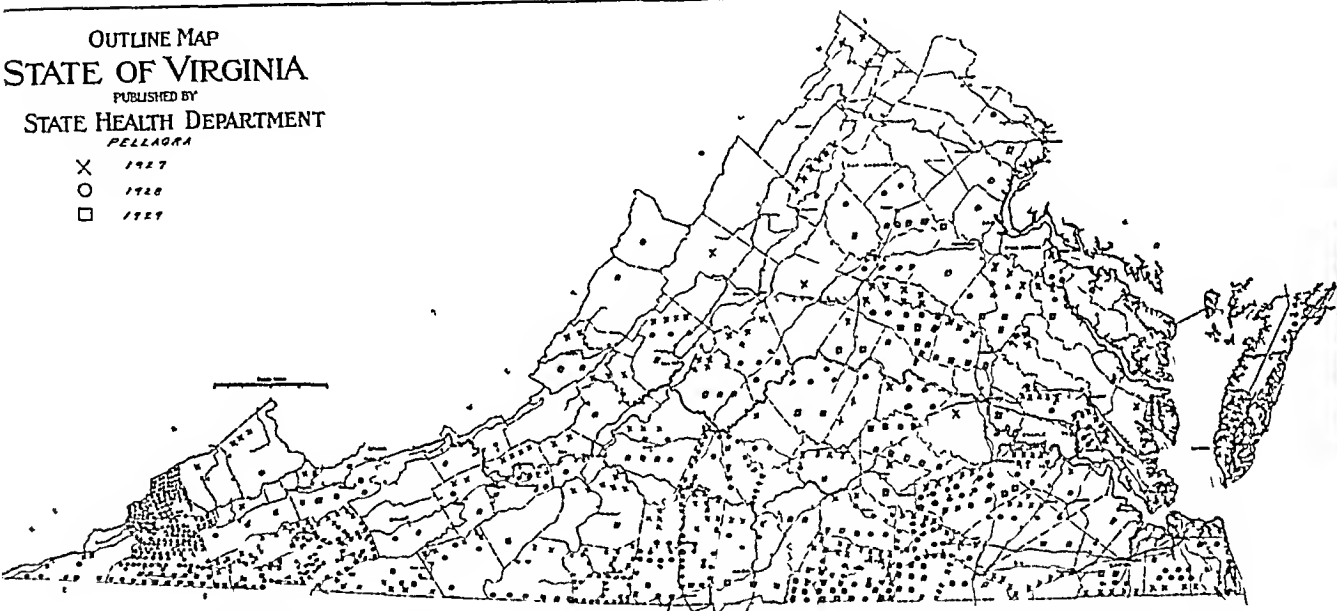


Chart 25—Incidence and distribution of pellagra in Virginia in 1927, 1928 and 1929 (From the Virginia State Board of Health)

deficit below 70 per cent but not as much as 10 per cent (Florida and California), there were less than 100 cases of pellagra per state reported

⁴ All data relative to the incidence, distribution and prevalence of pellagra in the United States are derived from the United States Public Health Reports and reports of the State Boards of Health. While the data are based chiefly on returns from practicing physicians and are generally conceded to be incomplete, there appears to be a probability of average error which would equalize the application of the figures. In instances in which careful enumeration has been made by official agencies (Hygienic Laboratory Bulletin, reference 45), the data are in general agreement with those from the sources generally used herein. Statistics gathered by direct observation, as those of the Hygienic Laboratory, would be expected to represent more accurately the actual development of the disease than reports compiled from the data furnished by practicing physicians, however, there is but little noticeable variation between the seasonal incidence as represented by the two classes of statistics.

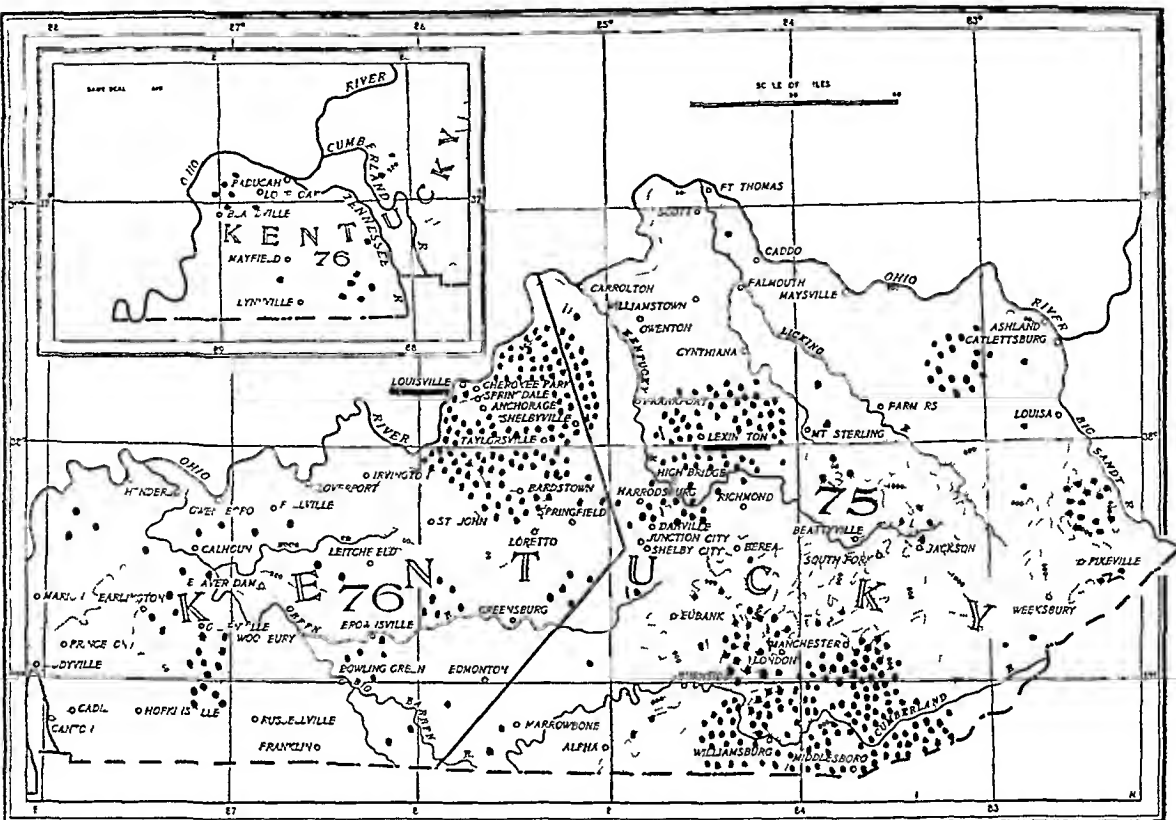


Chart 26—Incidence and distribution of pellagra in Kentucky from 1907 to 1911, inclusive (After Lavinder)

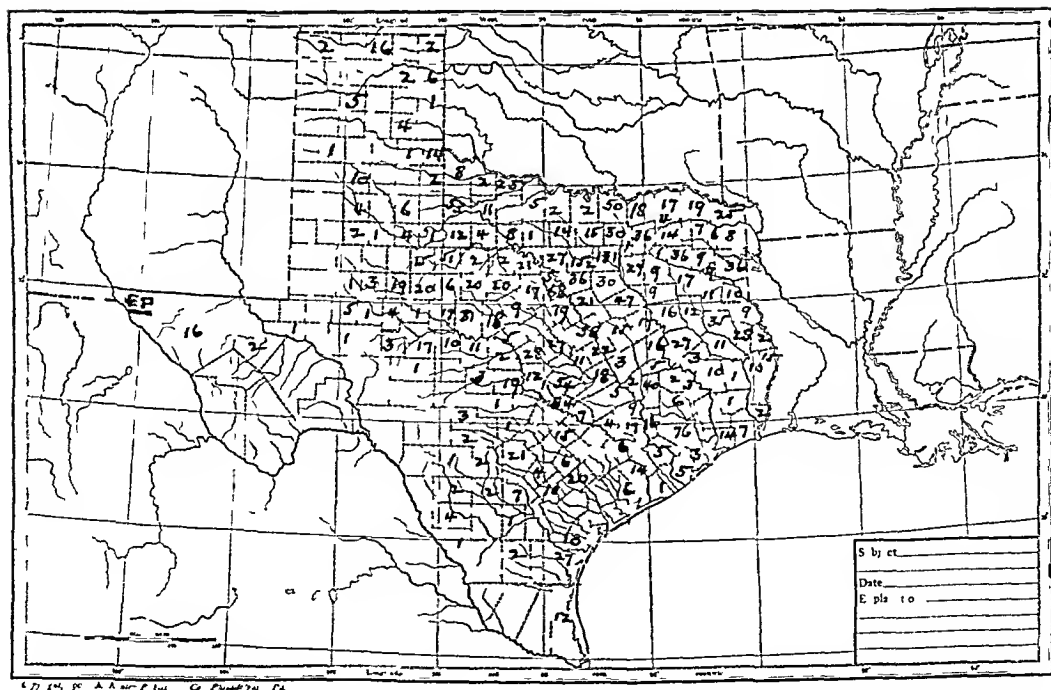


Chart 27—Incidence and distribution of pellagra in Texas, from 1907 to 1911, inclusive (After Lavinder)

in any year from 1926 to 1928, inclusive, and that in areas where there was a deficit of winter sunshine of from 10 to 27 per cent below the standard of 70 per cent (from the Atlantic coast to longitude 101° W), there were 500 or more cases of pellagra per state for each of the years 1926, 1927 and 1928

THE SEASONAL INCIDENCE OF PELLAGRA IN NINE SOUTHERN STATES, FROM 1925 TO 1929, INCLUSIVE, IN RELATION TO SOLAR RADIATION

The data on the seasonal incidence of pellagra in nine southern states are plotted in charts 28 to 69*. The relatively low incidence of pellagra in Florida and California (less than 100 cases a year reported) renders

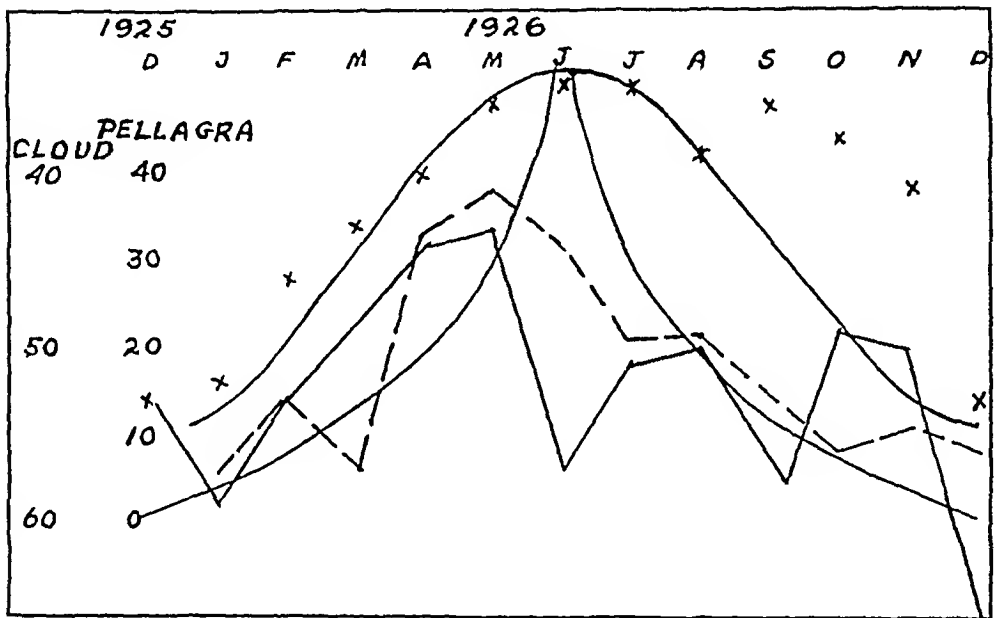


Chart 28—Virginia, 1926 In this chart and charts 29 to 60, \times indicates the average sunshine at all stations for the period of observation. The continuous curves indicate the curve of the angle of the sun. The two continuous curves indicate the curve of the air mass or air filter. The continuous line indicates the average of cloudiness at all stations, the broken line, the monthly incidence of pellagra.

them unsuitable for purposes of statistical study, and they are excluded from general statements.

The striking feature of the charts is the tendency for the seasonal incidence of pellagra to rise and fall with the decreasing and increasing air filter, if the curve of ultraviolet intensity at Davos is considered as applicable to these states, the tendency is for the seasonal incidence of pellagra to rise and fall with increasing and decreasing intensity of

* The curve of the percentage of cloudiness for each state was obtained as a result of the average of all stations reporting from the state.

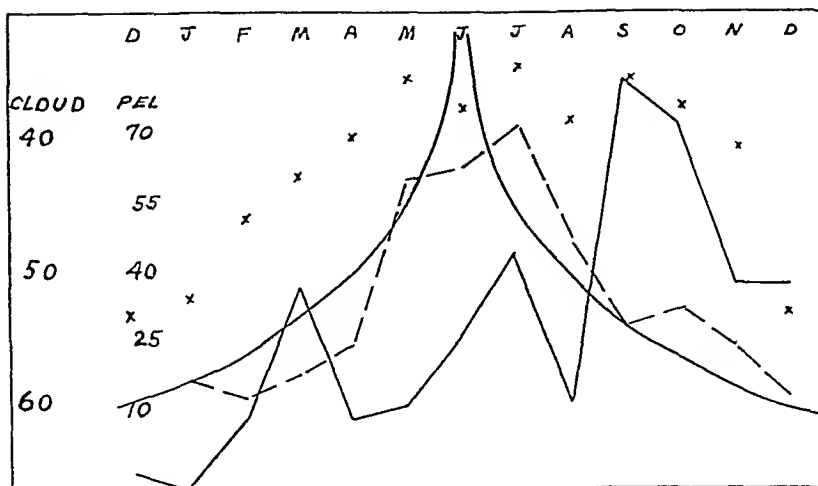


Chart 29—Virginia, 1927

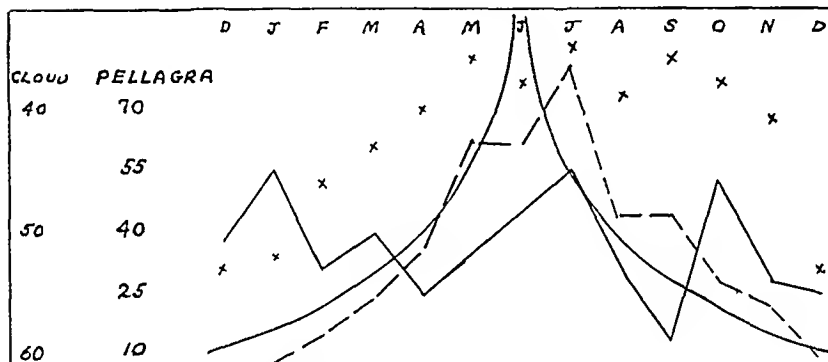


Chart 30—Virginia, 1928

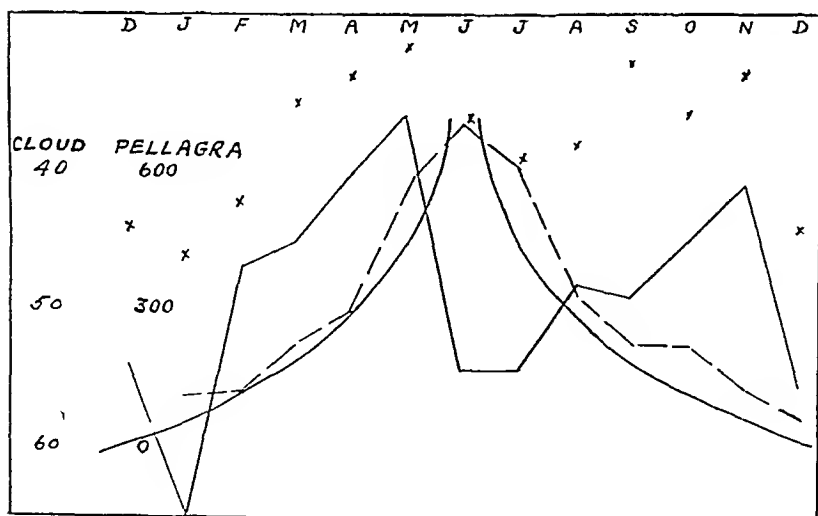


Chart 31—South Carolina, 1926

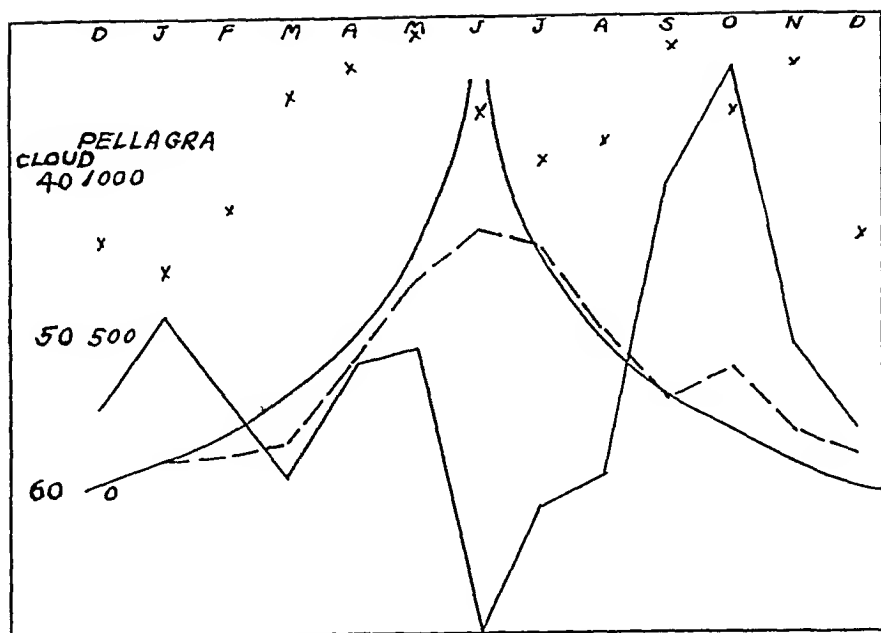


Chart 32—South Carolina, 1927

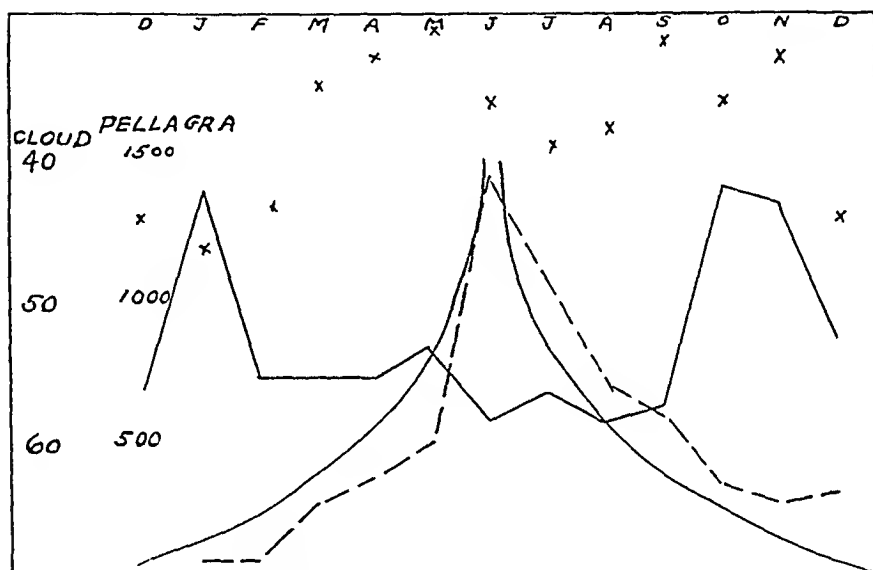


Chart 33—South Carolina, 1928

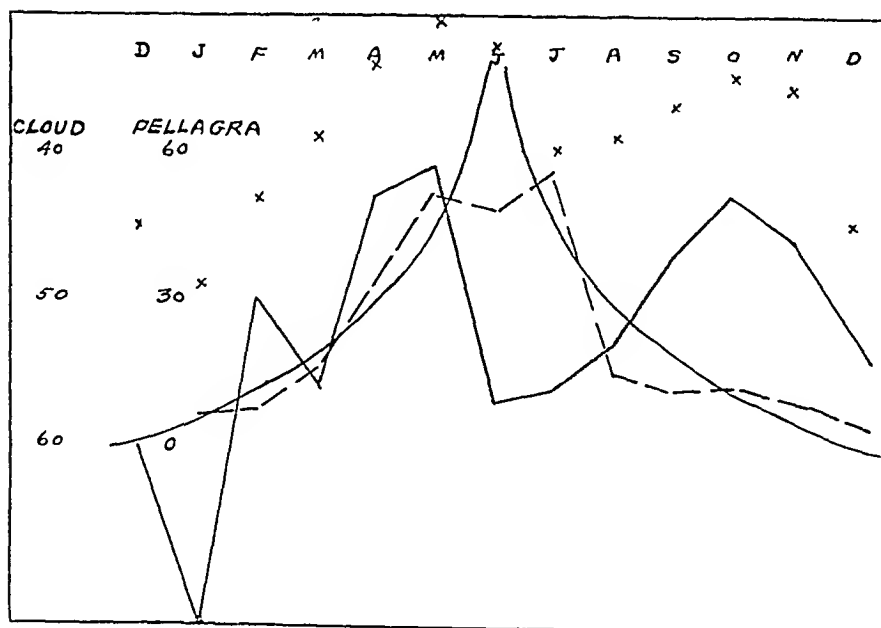


Chart 34—Georgia, 1926

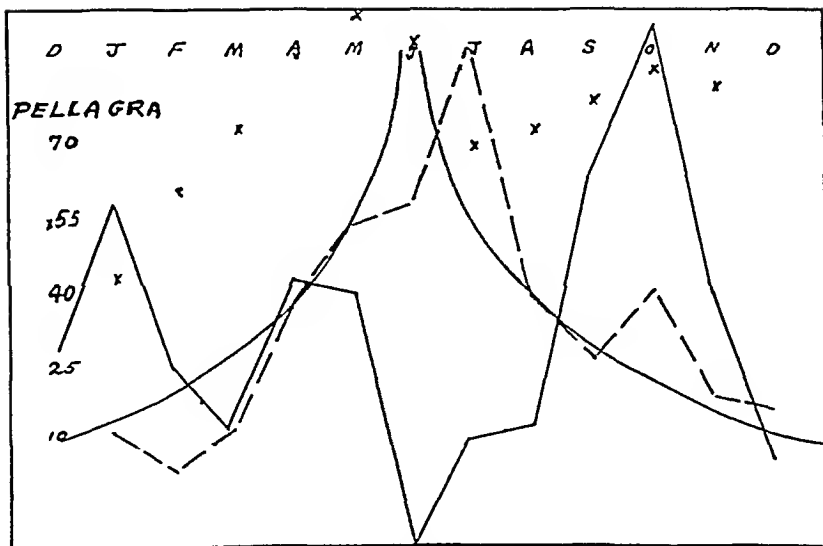


Chart 35—Georgia, 1927

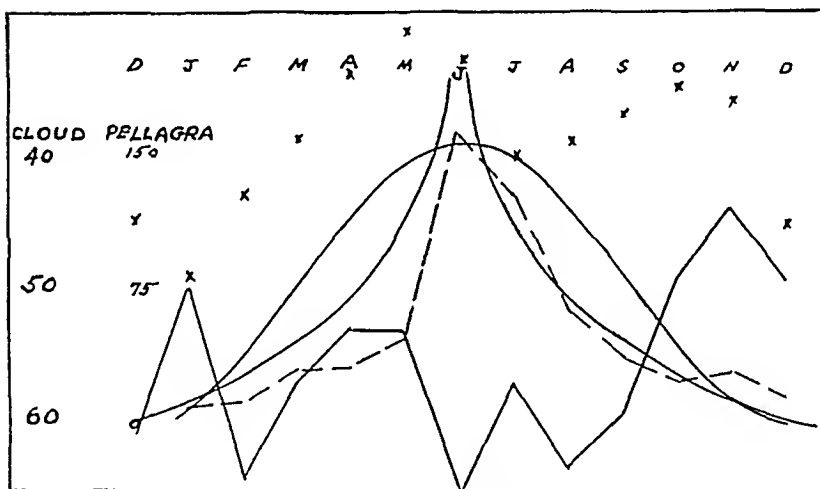


Chart 36—Georgia, 1928

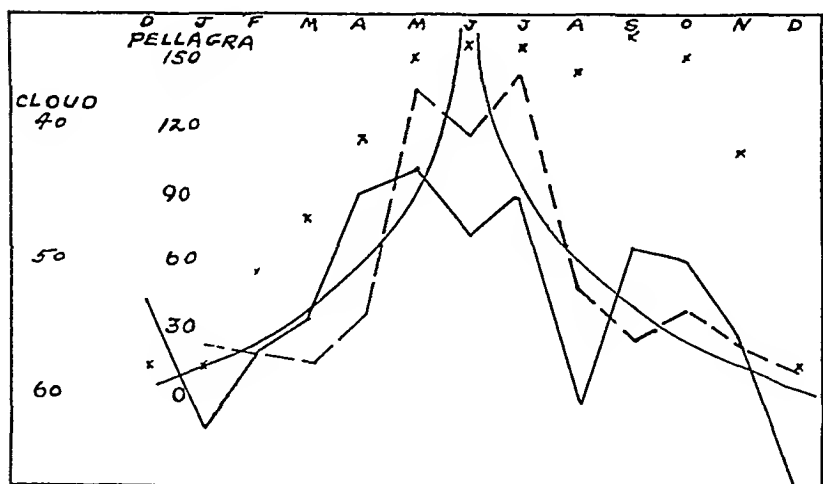


Chart 37—Tennessee, 1926

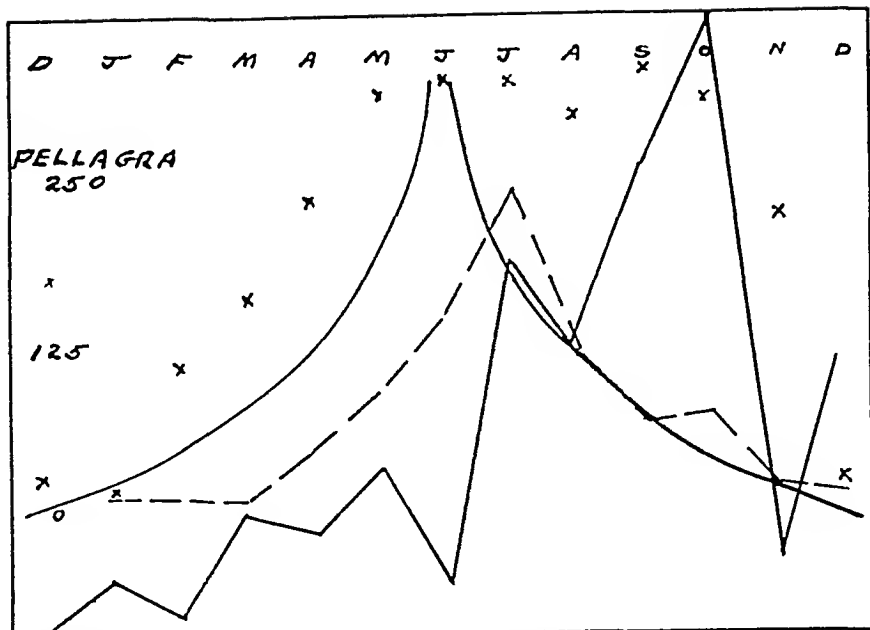


Chart 38—Tennessee, 1927

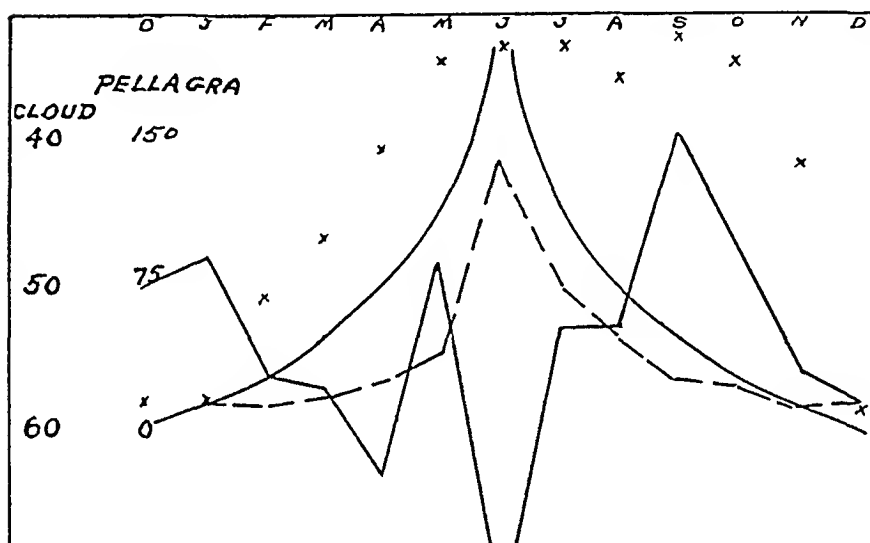


Chart 39—Tennessee, 1928

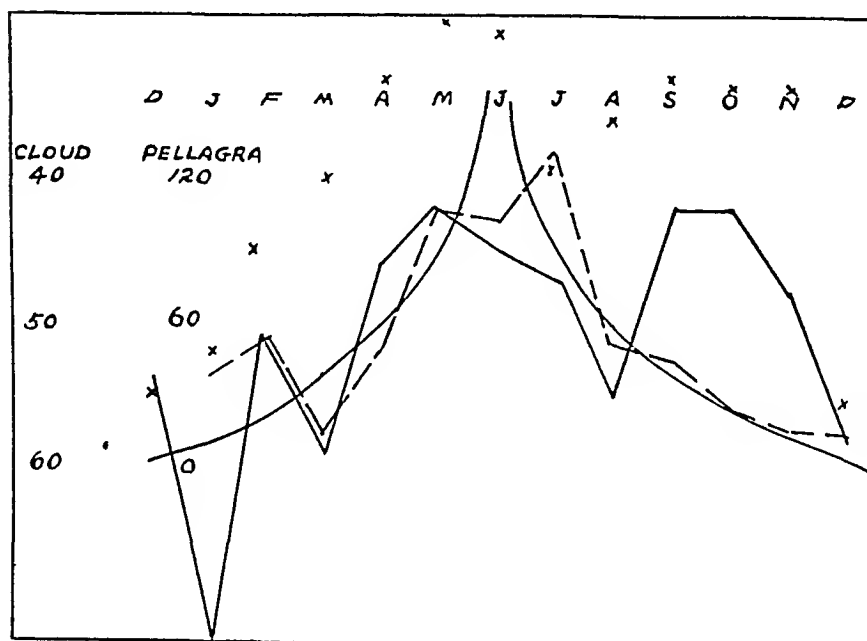


Chart 40—Alabama, 1926

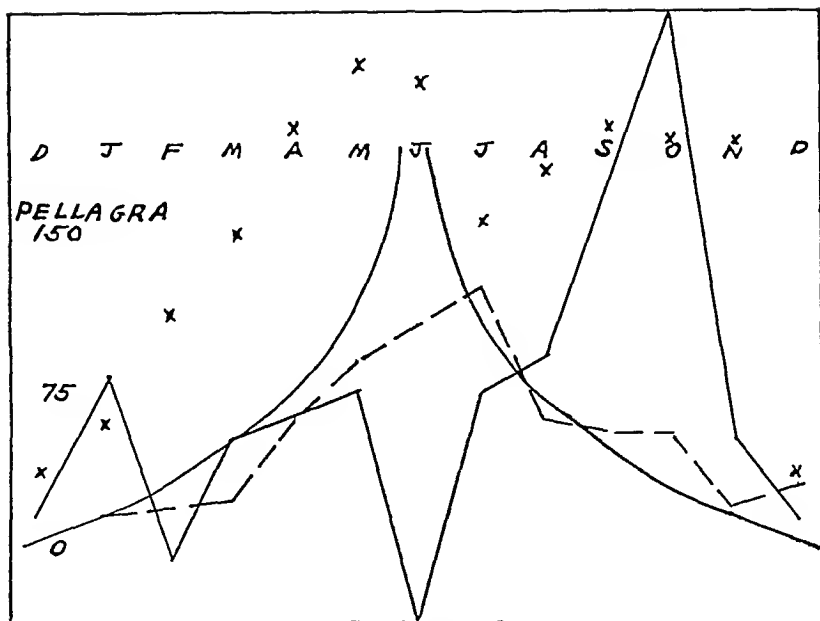


Chart 41—Alabama, 1927

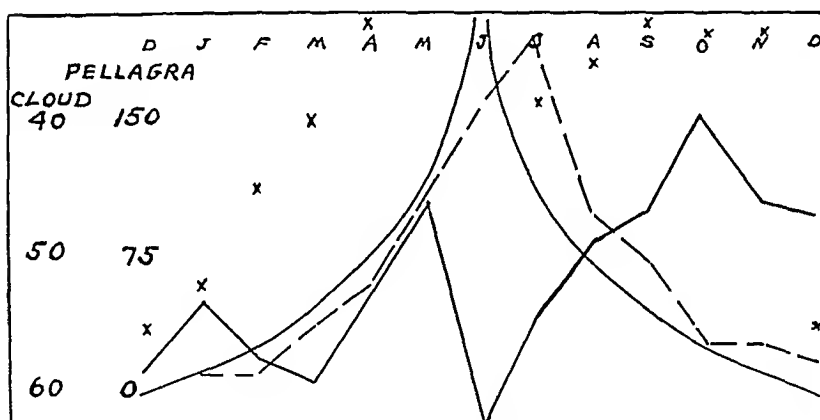


Chart 42—Alabama, 1928

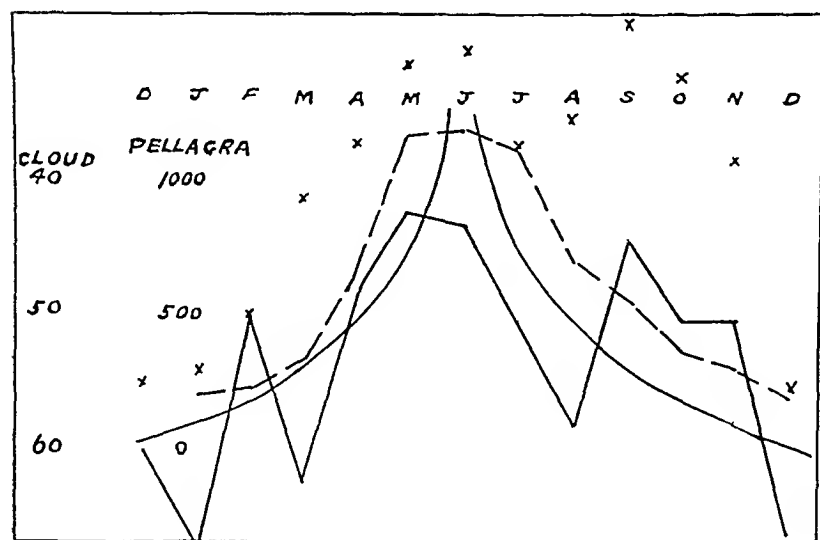


Chart 43—Mississippi, 1926

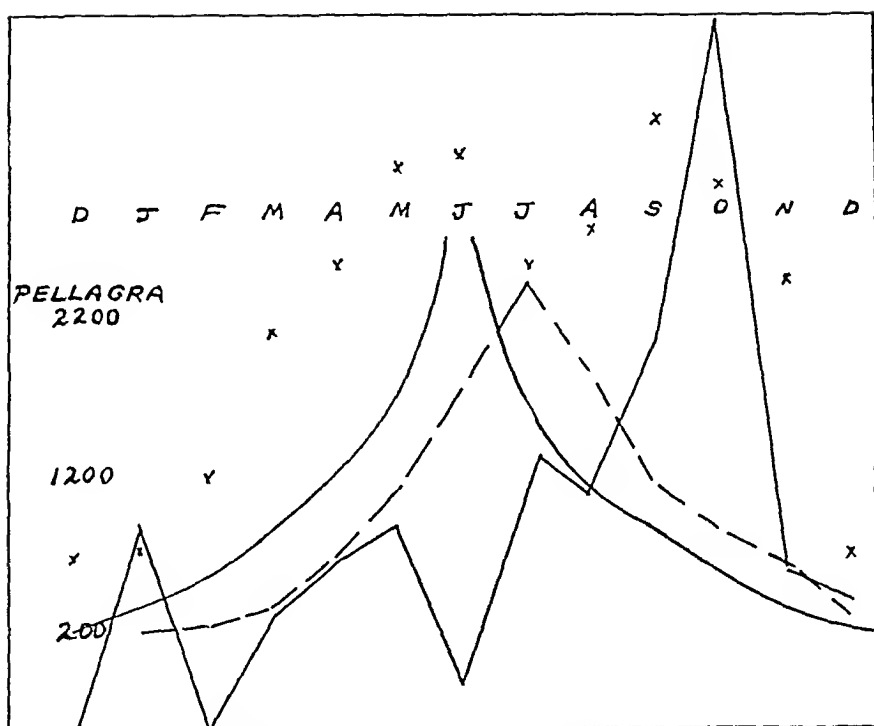


Chart 44—Mississippi, 1927

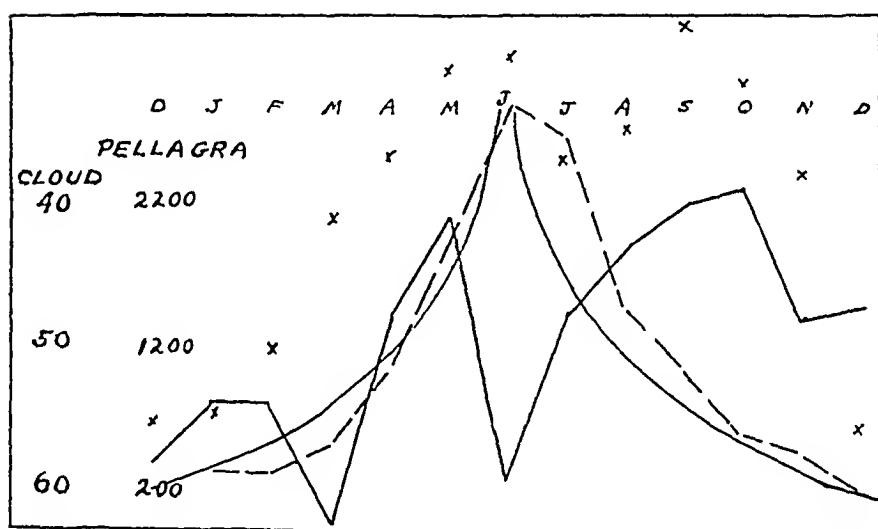


Chart 45—Mississippi, 1928

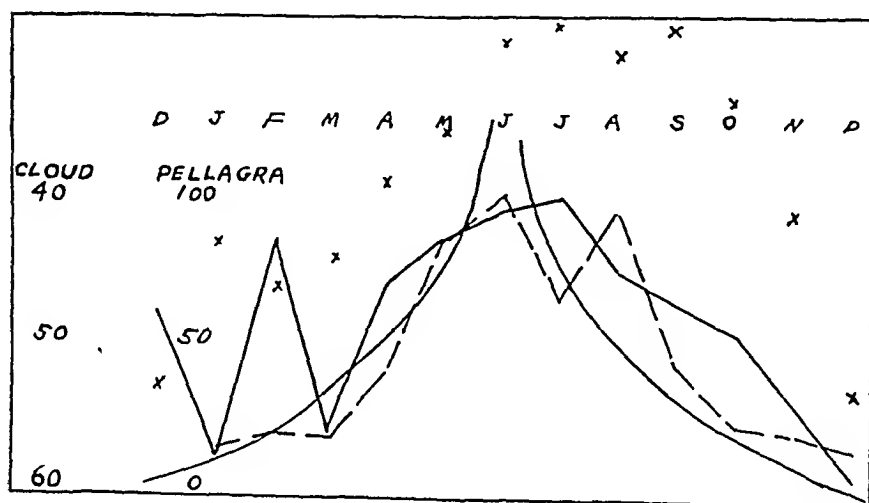


Chart 46—Arkansas, 1926

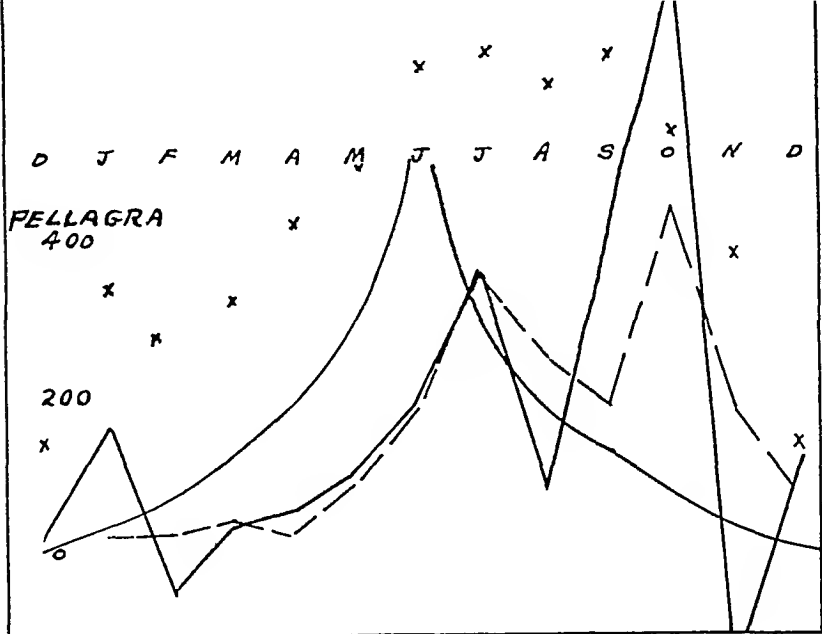


Chart 47 —Arkansas, 1927

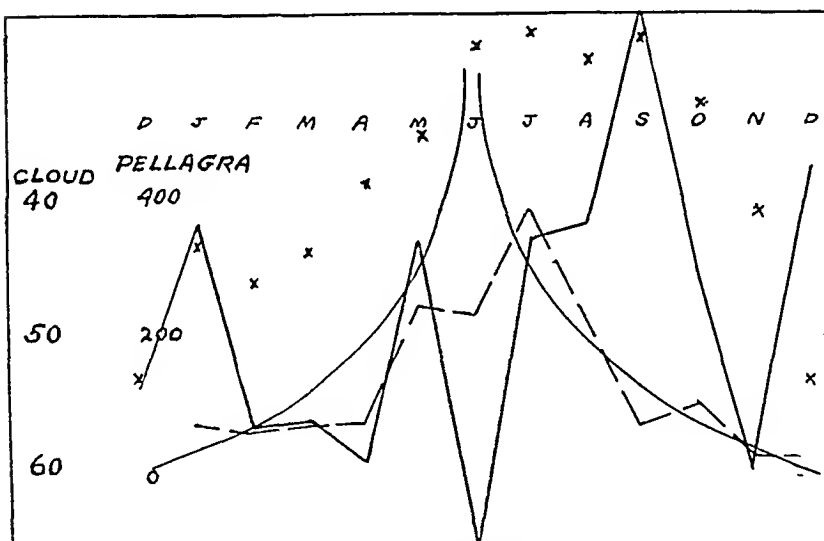


Chart 48 —Arkansas, 1928

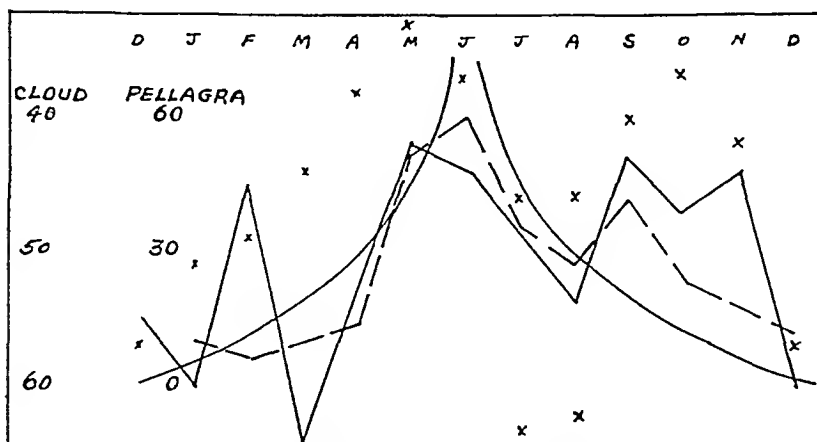


Chart 49 —Louisiana, 1926

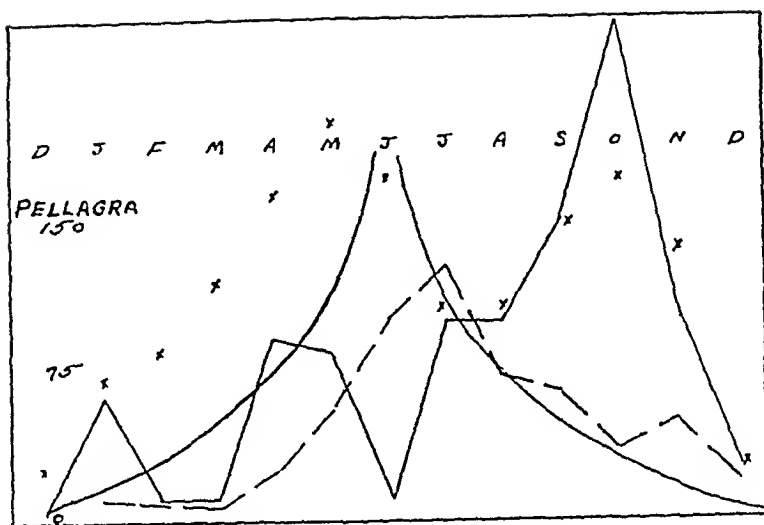


Chart 50—Louisiana, 1927

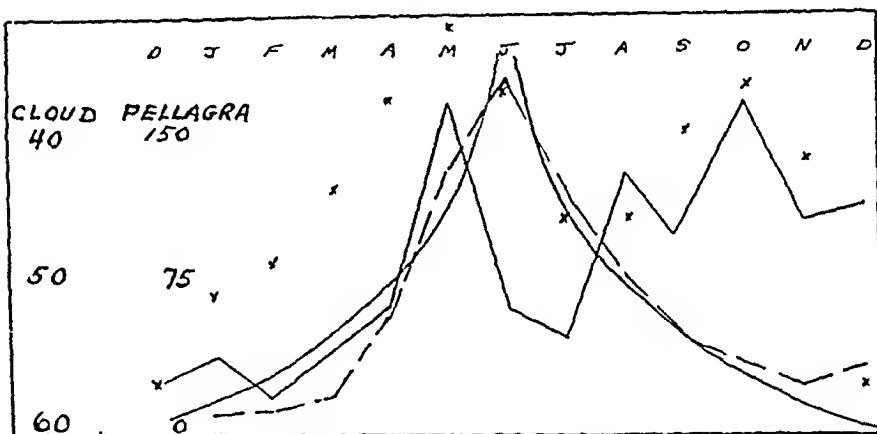


Chart 51—Louisiana, 1928

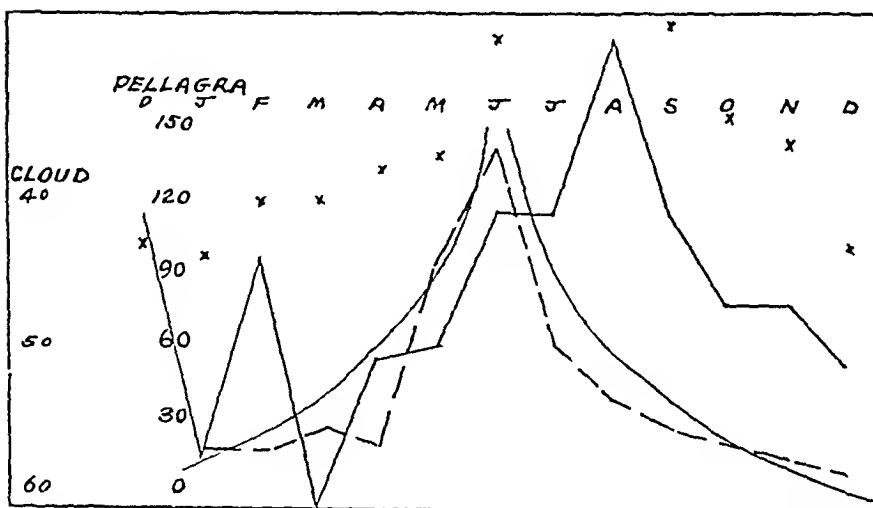


Chart 52—Oklahoma, 1926

ultraviolet radiation, or, if the curve tentatively presented as that of the average basal metabolism in Virginia is considered as applicable generally to the southern part of the United States, the tendency is for the seasonal incidence of pellagra to rise and fall in the direction opposite the rise and fall of the average basal metabolism* The larger the number of cases of pellagra in a given state for a given year, the closer these parallels tend to be †

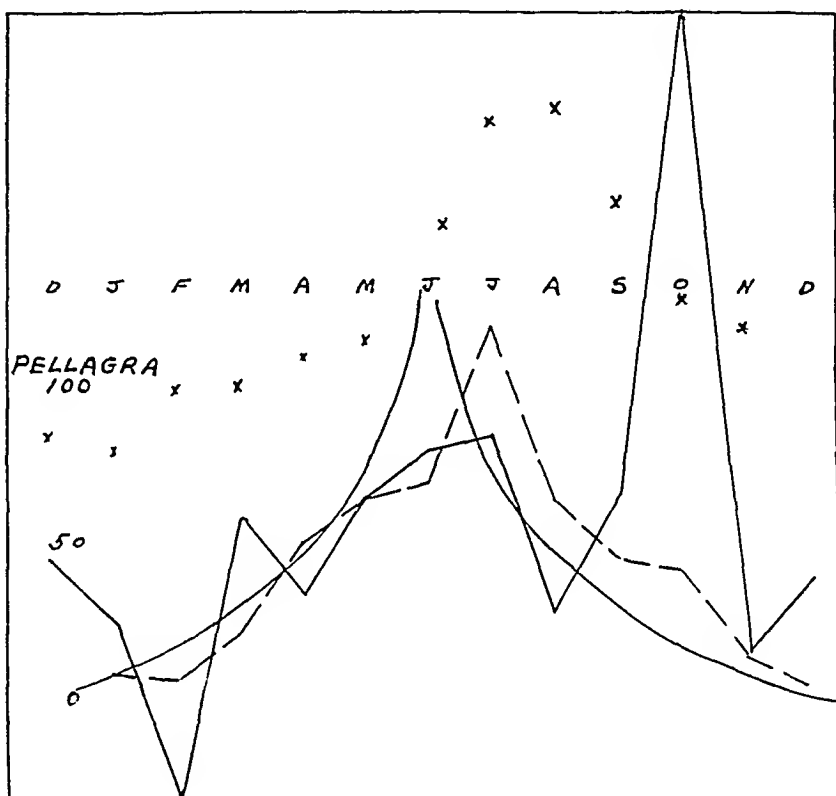


Chart 53—Oklahoma, 1927

Any comment on the seasonal character of pellagra should take into account the careful investigation of this and other features of the subject that has been made and published by the United States Public Health Service. In a study carried out in twenty-four cotton-mill

* A low average metabolic rate would appear to be less important in the etiology of pellagra than the relation of radiation during the winter to that during the summer, otherwise, there is reason to believe that pellagra would be more common in the tropics than in the southern part of the United States.

† The data for the incidence of pellagra were taken from the United States Public Health Reports. A few omissions were supplied by estimate. As a rule the early months of the year appear to furnish a fairly reliable index to the total number of cases for the year.

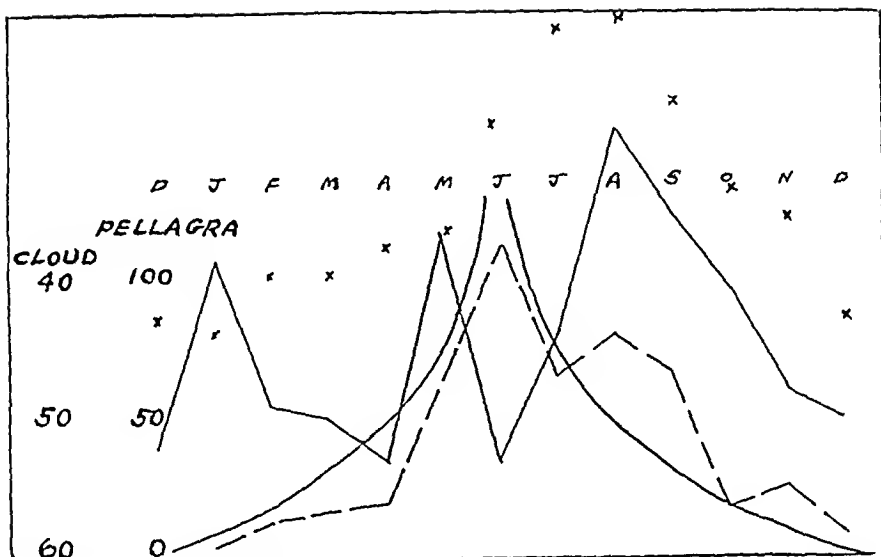


Chart 54 —Oklahoma, 1928

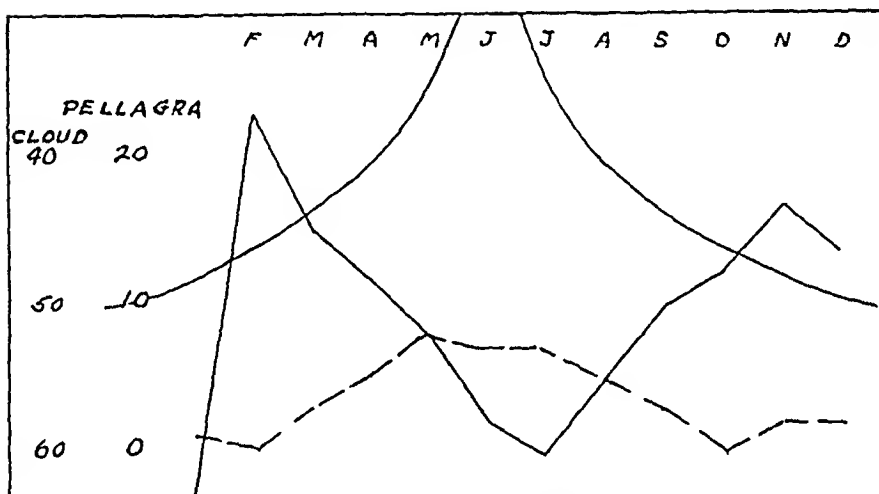


Chart 55 —Florida, 1926

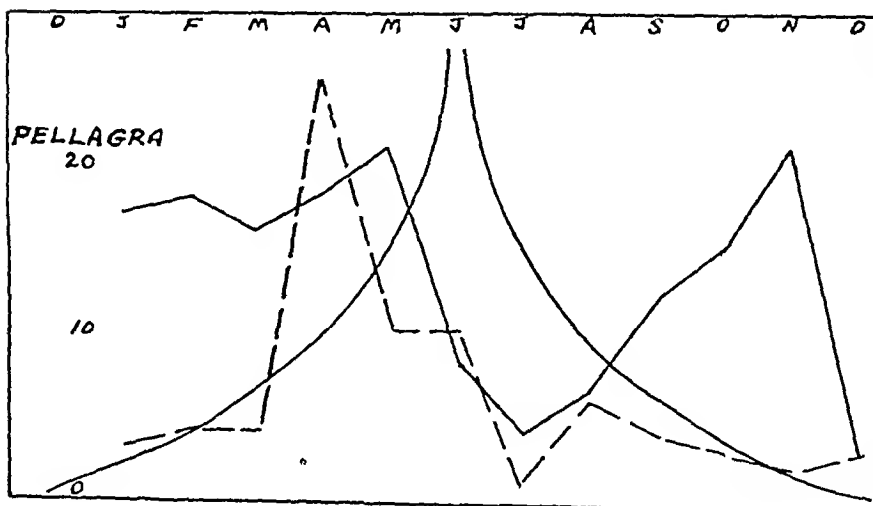


Chart 56 —Florida, 1927

villages in South Carolina, from 1916 to 1921 ⁴⁵—which will be referred to hereafter as the Hygienic Laboratory report—the authors of this report stated that

Our findings as they relate to the general curve of the seasonal incidence of the disease agree with those of the earlier students in the same locality, as they

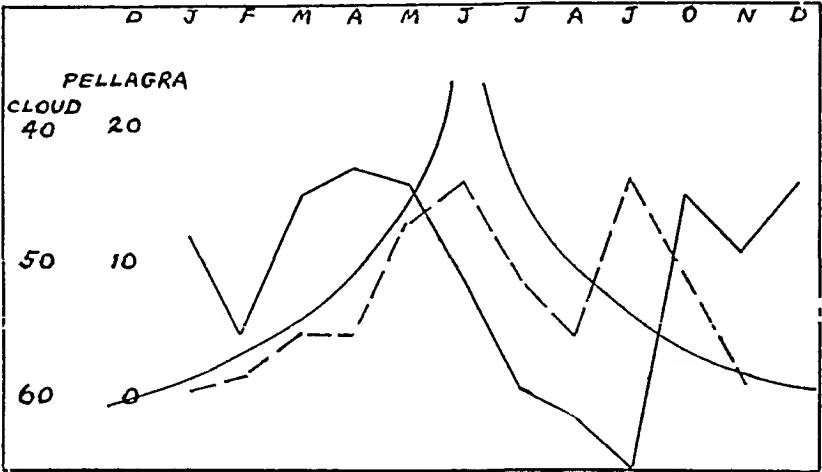


Chart 57—Florida, 1928

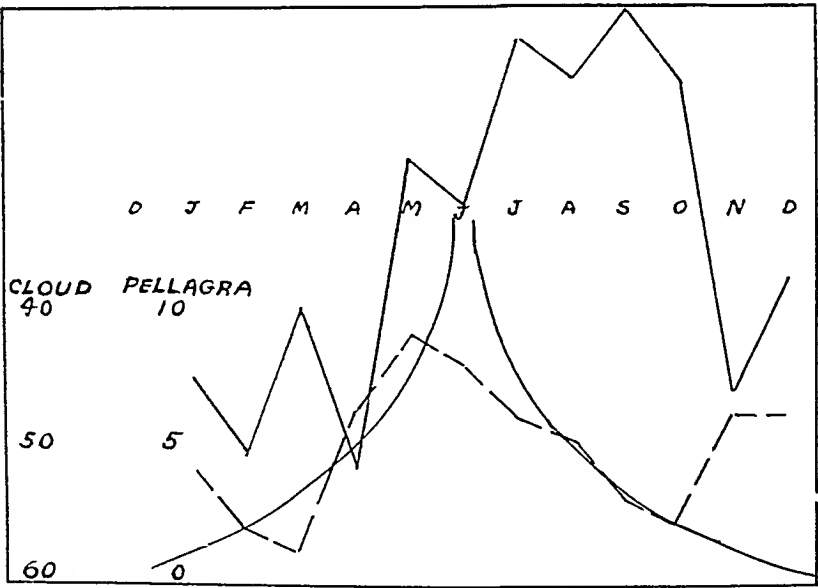


Chart 58—California, 1926

do also with the general experience of observers in other localities in the North Temperate Zone, both American and European (p 33)

Chart 70 reproduces the curve representing the experience of these investigators, which they described as follows

The incidence of the disease for the twenty-four villages may, therefore, be considered as describing a curve, the outstanding features of which would seem

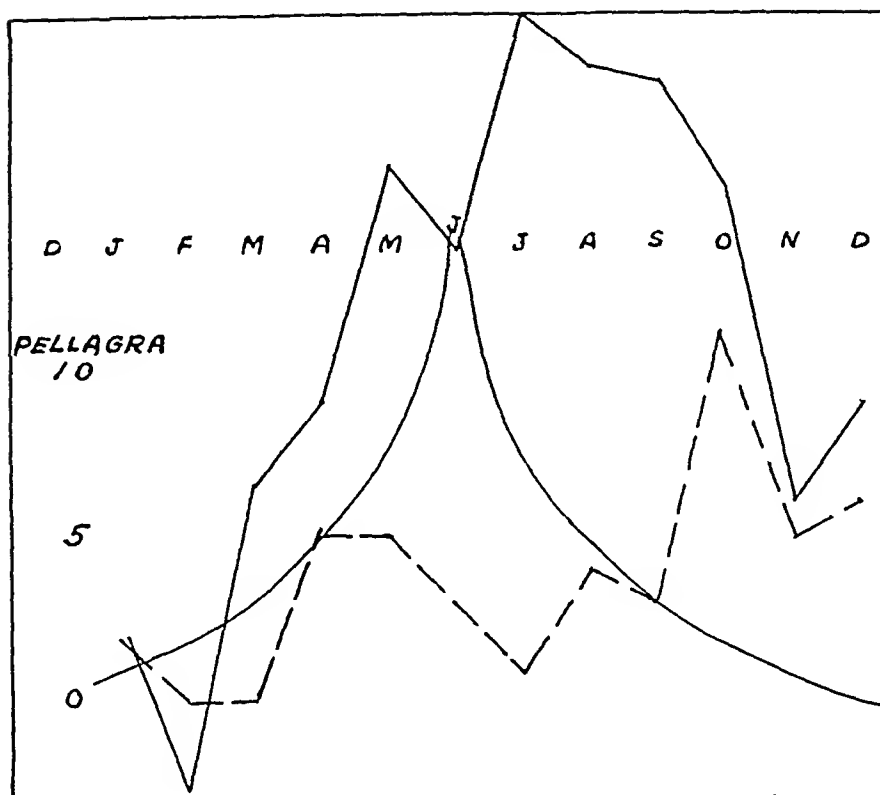


Chart 59—California, 1927

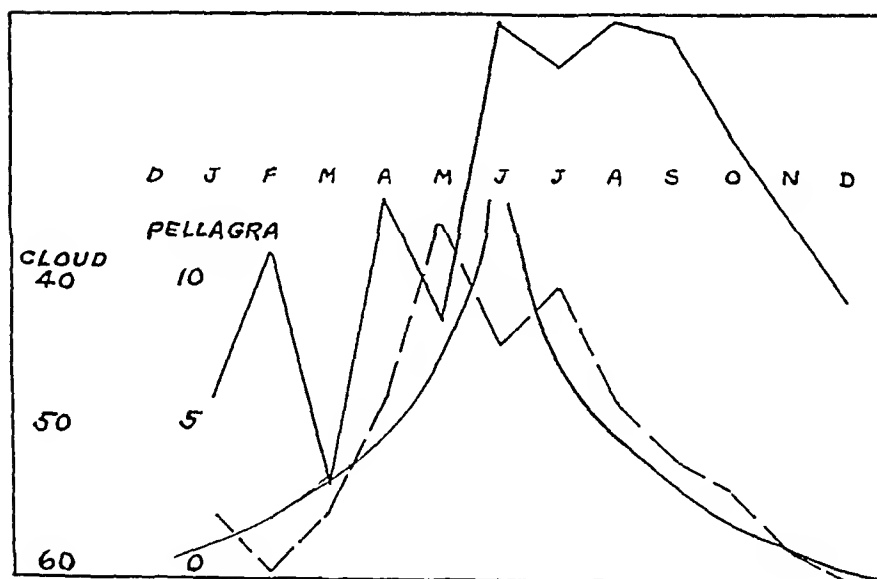


Chart 60—California, 1928



Chart 61—Virginia, from 1925 to 1929, inclusive The continuous line indicates the average of cloudiness at all stations, the broken line, the monthly incidence of pellagra, the line in reversed parentheses, the summer season, the sun being north of the equator

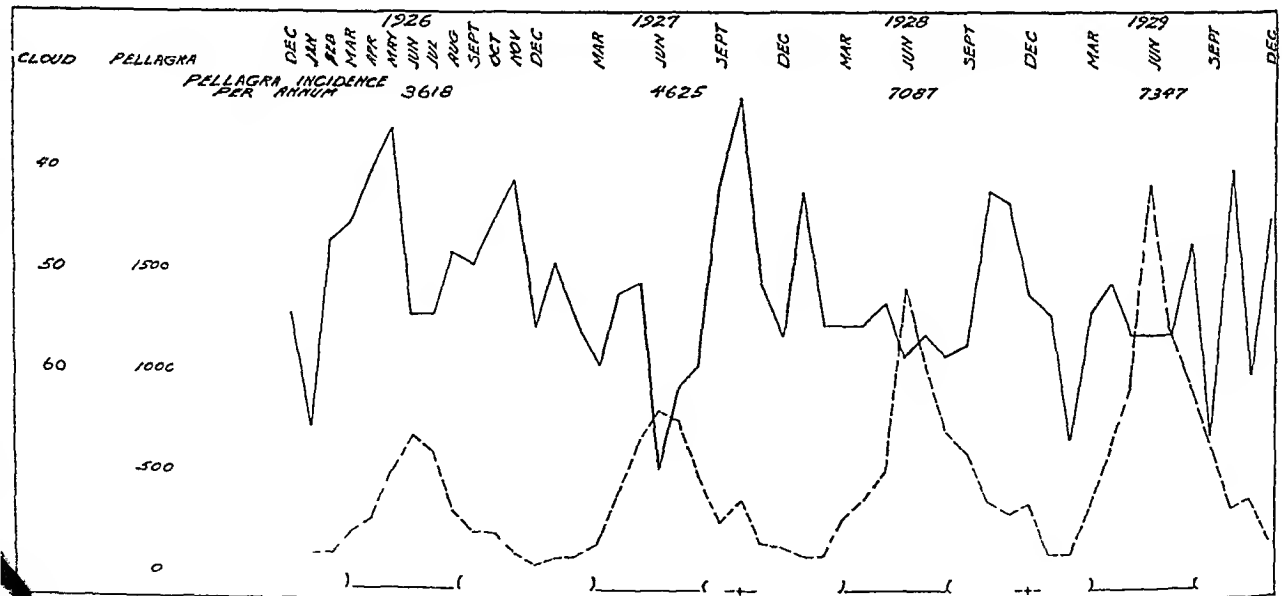


Chart 62—South Carolina, from 1926 to 1929, inclusive The continuous line indicates the average of cloudiness at all stations, the broken line, the monthly incidence of pellagra, the line in reversed parentheses, the summer season, the sun being north of the equator, the dash, plus, dash line the secondary peak in the incidence of pellagra coincident with excess sunshine

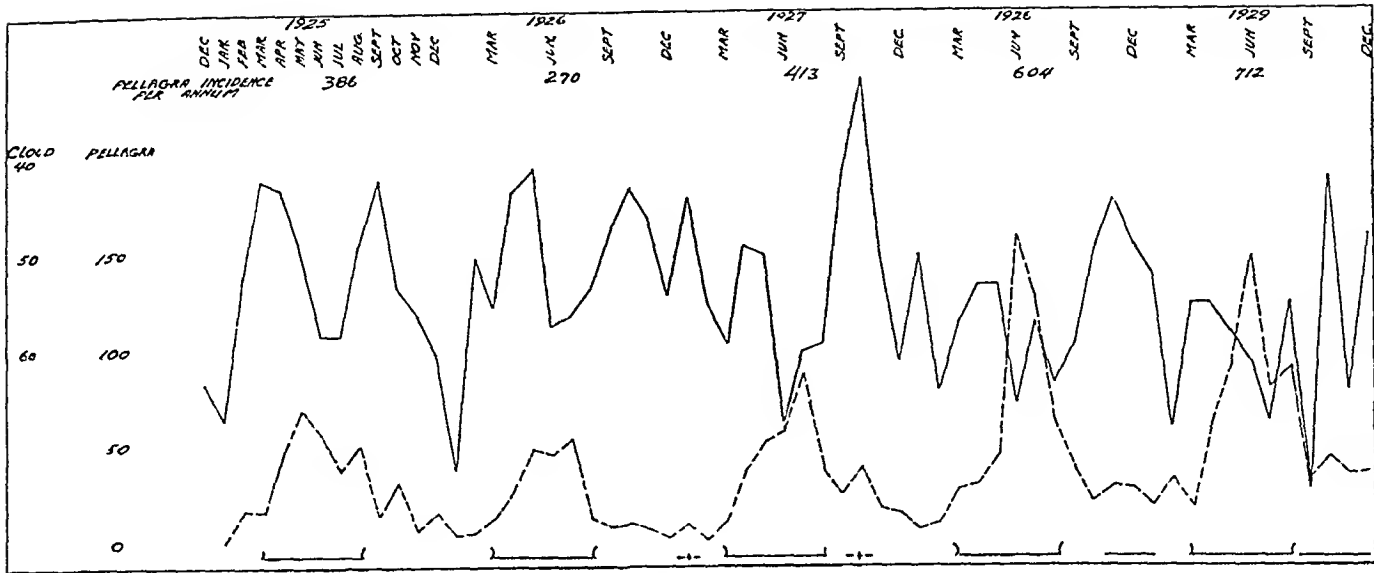


Chart 63—Georgia, from 1925 to 1929, inclusive. The continuous line indicates the average of cloudiness at all stations, the broken line, the monthly incidence of pellagra, the line in reversed parentheses, the summer season, the sun being north of the equator, the dash, plus, dash line, the secondary peak in the incidence of pellagra coincident with excess sunshine.

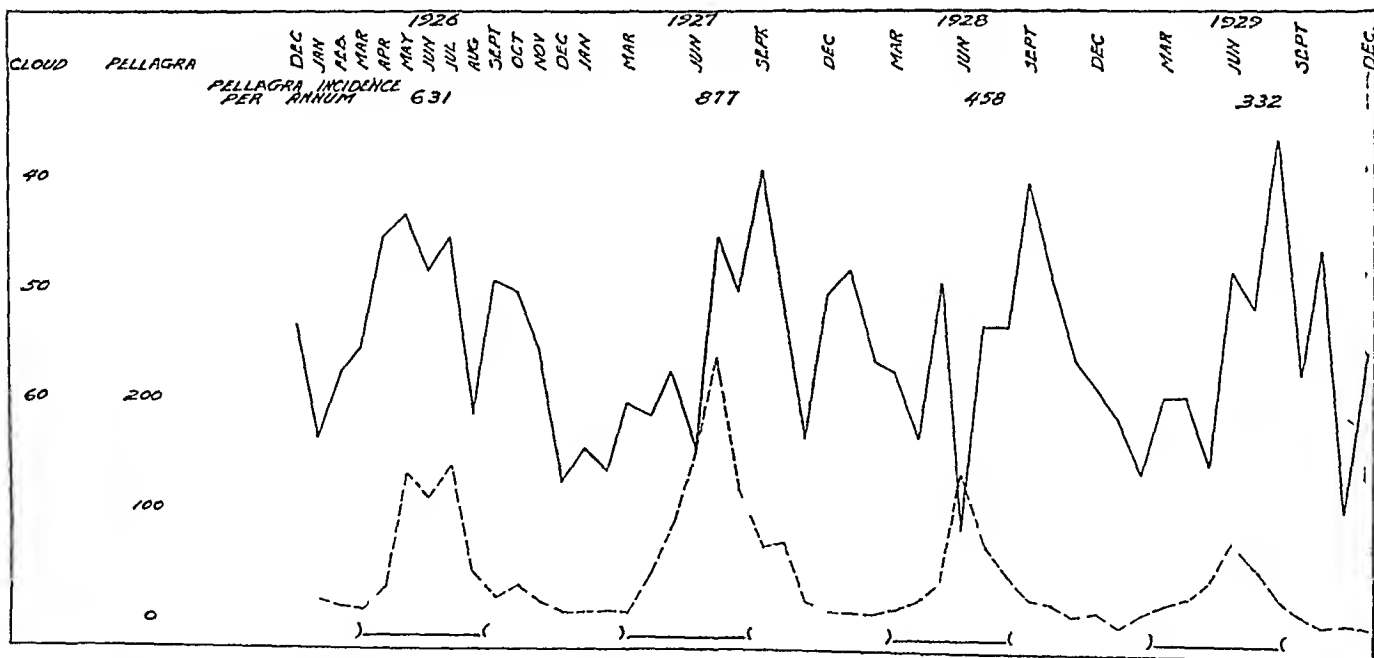


Chart 64—Tennessee, from 1926 to 1929, inclusive. The continuous line indicates the average of cloudiness at all stations, the broken line, the monthly incidence of pellagra, the line in reversed parentheses, the summer season, the sun being north of the equator.

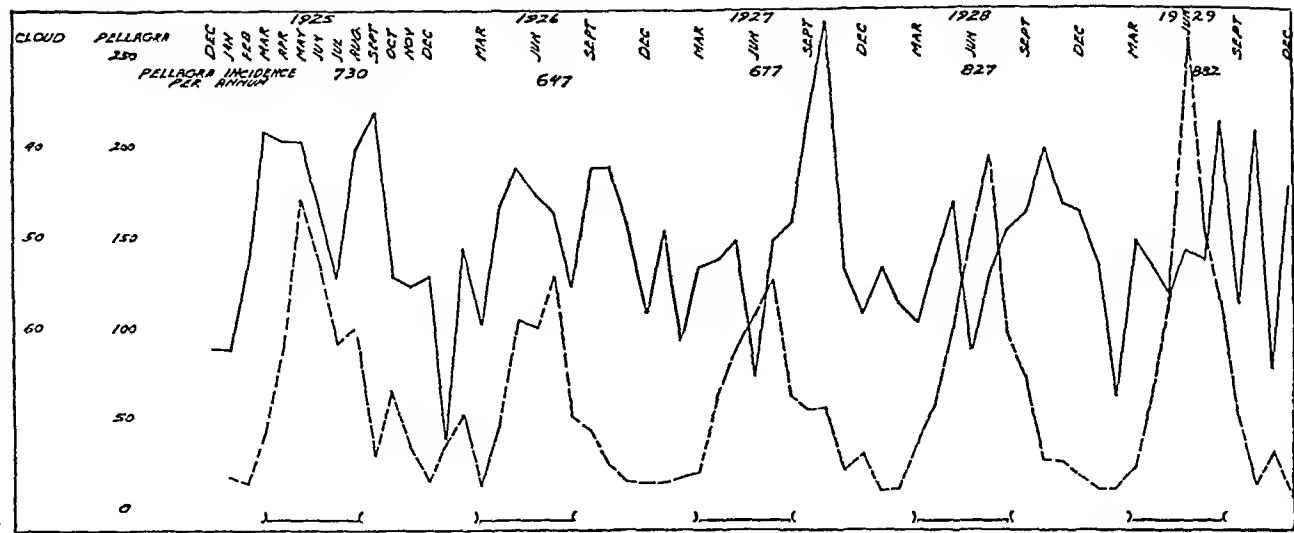


Chart 65—Alabama, from 1925 to 1929, inclusive. The continuous line indicates the average of cloudiness at all stations, the broken line, the monthly incidence of pellagra, the line in reversed parentheses, the summer season, the sun being north of the equator.

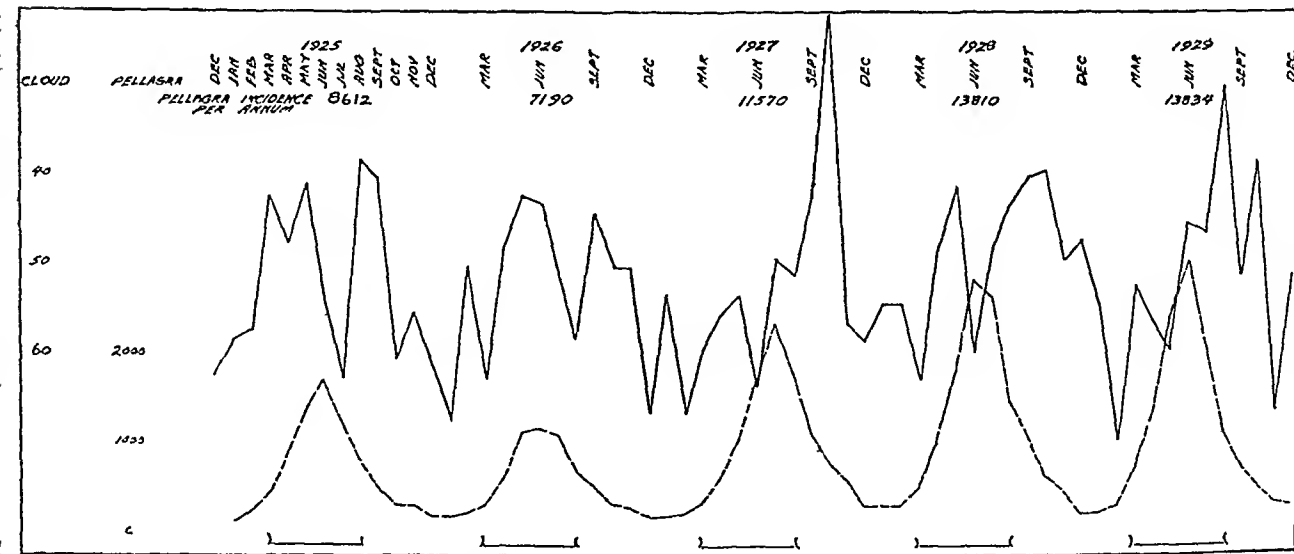


Chart 66—Mississippi, from 1925 to 1929, inclusive. The continuous line indicates the average of cloudiness at all stations, the broken line, the monthly incidence of pellagra, the line in reversed parentheses, the summer season, the sun being north of the equator.

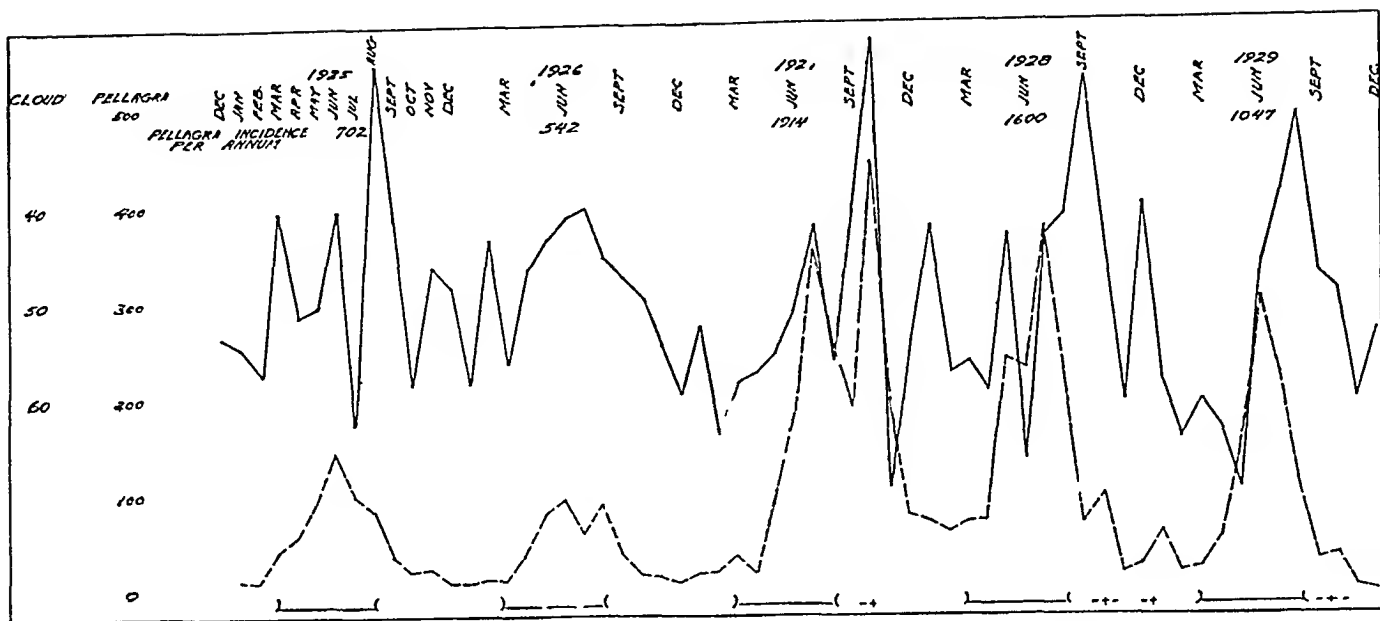


Chart 67—Arkansas, from 1925 to 1929, inclusive The continuous line indicates the average of cloudiness at all stations, the broken line the monthly incidence of pellagra, the line in reversed parentheses, the summer season, the sun being north of the equator, the dash, plus, dash line, the secondary peak in the incidence of pellagra coincident with excess sunshine

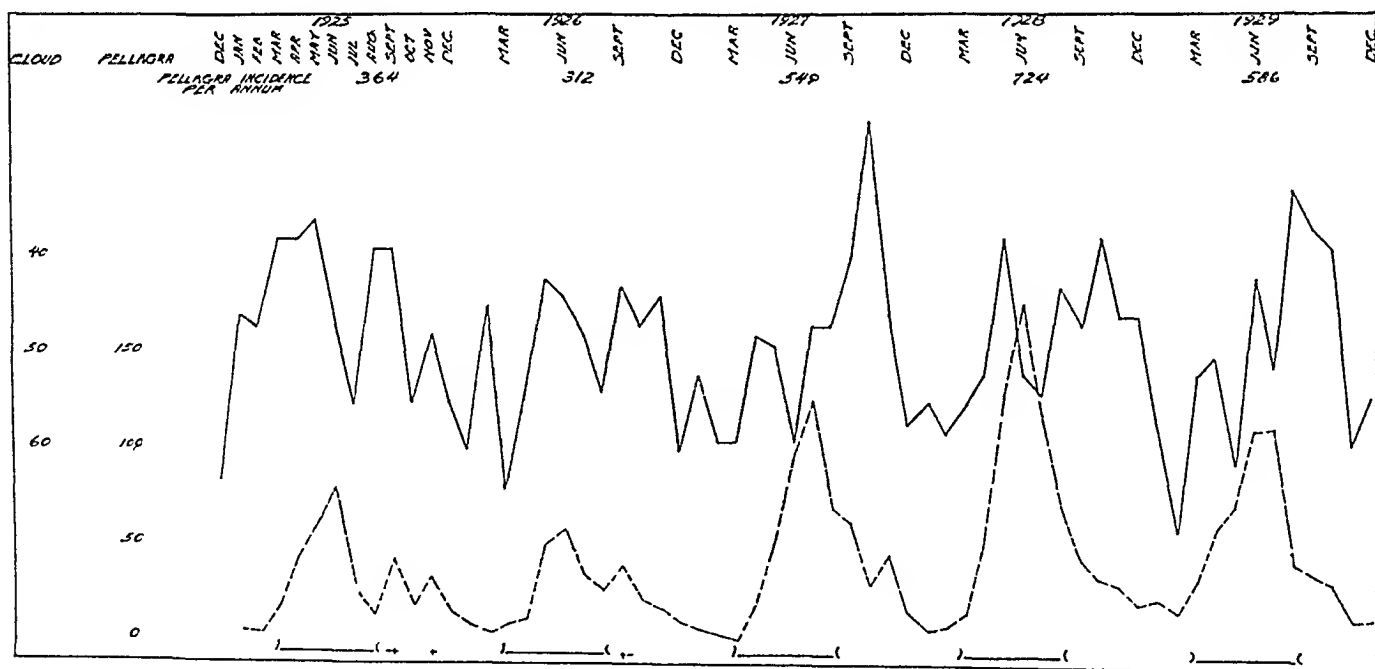


Chart 68—Louisiana, from 1925 to 1929, inclusive The continuous line indicates the average of cloudiness at all stations, the broken line, the monthly incidence of pellagra, the line in reversed parentheses, the summer season, the sun being north of the equator, the dash, plus dash line, the secondary peak in the incidence of pellagra coincident with excess sunshine

to be its beginning with March, a steep rise during April and May to a sharp peak in the early part of June, followed by an even more precipitate fall beginning during the latter part of that month, continued through July and August, and the termination with September or during October

Continuing the discussion,⁴⁵ these authors stated

The extraordinarily marked seasonal character of the endemic disease would therefore seem to be a phenomenon related to an annually recurring factor or factors operating within wide geographical limits. In view of the proven dietary relation of the disease, it may be suggested that this annually recurring factor is probably the recurring variation in diet brought about by a seasonal modification of food supply which, in its turn, is probably the result of a variable complex of climatic and economic factors (p 33)

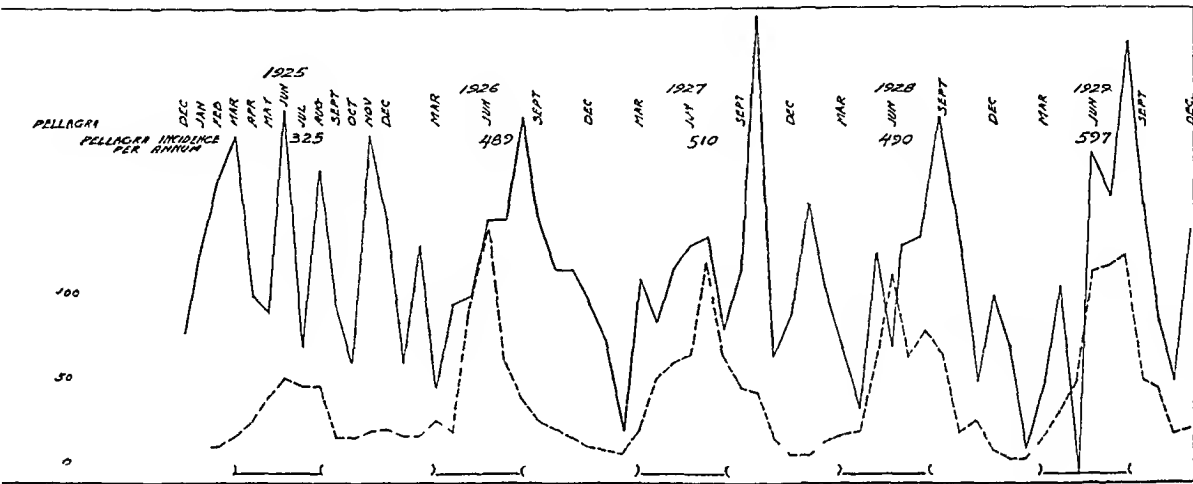


Chart 69—Oklahoma, from 1925 to 1929, inclusive. The continuous line indicates the cloudiness at Oklahoma City, the broken line, the monthly incidence of pellagra, the line in reversed parentheses, the summer season, the sun being north of the equator

The curves shown in charts 28 to 69 are therefore no exception to the general experience, and the fairly close parallel between the curves for the incidence of pellagra and for the air filter would suggest that the “annually recurring factor” is directly, and not indirectly, “climatic” and is not represented by a “recurring variation in diet” resulting from a variable complex

In a further discussion of the general curve of incidence, the investigators from the Hygienic Laboratory stated

Recurring variation in diet would explain the first part, the rise and upward course, of the curve of incidence as coming late in or immediately after, and due to a defective dietary period in the later part of the winter and of the early spring. It would explain the decline and cessation of incident cases as due to favorable modifications in diet associated with and following the changes in the food supply of the later part of the curve of seasonal incidence

In a footnote, it is observed "there are reports in the literature which would indicate that in some localities the curve of incidence may or has shown a second and much less marked peak in the late summer. This would appear to depend on factors of a less general character", (p 33) From an examination of charts 28 to 69, it would seem that this statement might be broadened to say that such a second and no less marked peak (chart 47, Arkansas, 1927) may occur as late as October.

According to charts 28 to 69, the peak of the incidence of pellagra is near the summer solstice. A secondary rise or peak following the summer solstice is not seen,⁴ except when there is a corresponding absence of cloudiness or a relative rise in the percentage of sunshine. In general, the curve for pellagra deviates from that for the air filter to correspond with excess sunshine (charts 32, 35, 37, 38, 41, 47, 50, 54,

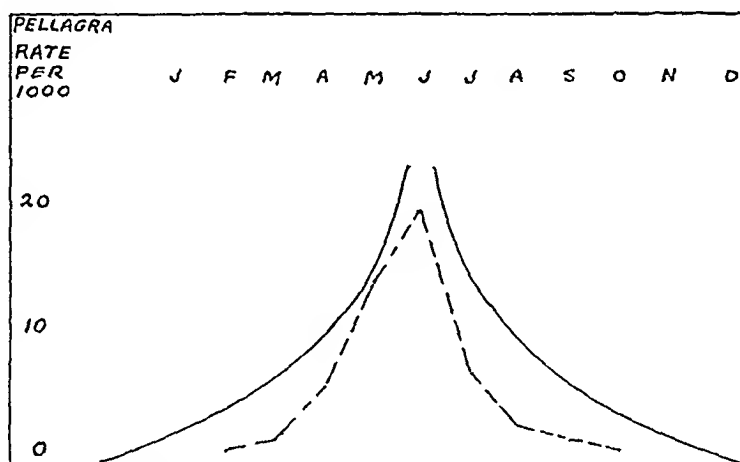


Chart 70—The broken line indicates the monthly incidence of pellagra in twenty-four villages of South Carolina in 1917 (From Hygienic Lab Bull, no 153)

62, 63, 67 and 68) Doubtless, as many persons have a tissue metabolism favorable to the development of pellagra in August as in either July or September, but they lack whatever influence there may be in a relatively greater solar radiation or irradiation[†] A limitation in intensity in solar radiation in the autumn is imposed by the declining angle of the sun's rays, apparently reflected in the autumnal incidence of pellagra both in cotton-mill workers and in the rural population. The almost complete cessation of the incidence of pellagra in the cotton-

Arkansas, 1926 (chart 46), is an exception, but the seasonal curve of the percentage of cloud also appears to be exceptional. There is also the possibility that a particular explanation is applicable, as in the instance of August, 1921, in Arkansas.

[†] There is a tendency among farmers who raise cotton to "ease off" in attention to the crop in August (Vance, reference 110)

mill villages during the late fall and winter months and the continuation of a relatively low but definite incidence in rural populations suggest a positive influence of exposure to the sun's rays in the latter group (The autumn peak in sunshine apparently must have both height and breadth in order to effect an autumn rise in pellagra)

In the Hygienic Laboratory report careful attention is given the "peak month" in the various villages studied, and on the basis of the chronological position of the peak of incidence, the villages fall into three groups ⁴⁵ The authors noted

As is clearly evident, the outstanding differences in seasonal distribution of "onset" relate practically altogether to the position of the peak, so that it would seem as if the factor or factors responsible for the development of the disease, although beginning to make themselves felt at about the same time in all three groups of villages, for some reason attained maximum force or began to be exhausted or both approximately a month sooner in the villages of two of the groups than in those of the third (p 28)

Reference to charts 28 to 69, as stated, shows that the peak of the incidence of pellagra occurs near the summer solstice. It may follow the summer solstice or it may precede it, but as far as the observations go it does not precede the peak of sunshine or the absence of cloudiness so far as this peak occurs prior to the summer solstice. If the peak of sunshine is reached in May or June, the peak of pellagra is reached in June, if the peak of sunshine is delayed till July, the peak of pellagra is delayed till July.

In regard to the question of the chronological position of the peaks in the villages mentioned in the Hygienic Laboratory report, it is interesting to compare, so far as the available data will permit, the chronological peak of the incidence of pellagra with the chronological peak of sunshine. United States Weather Bureau stations are located at Greenville and at Columbia. Since the location of the villages may be identified in the Hygienic Laboratory report (chart 91), they may be grouped with reference to their proximity to Greenville and Columbia, respectively, and the prevailing conditions of the weather as reported for these stations, respectively, may be used as the nearest available approximation to the conditions of the weather that prevailed in the groups of villages at the time studied.

For one village with a population of 803 in the Greenville area, the Hygienic Laboratory report gives data on the incidence of pellagra for five years, from 1917 to 1921 (charts 71, 72, 73, 74 and 75). For two villages (Gy and Ola) in the Columbia area (chart 76), data are published for 1917. For five villages (Dun, Jn, Fn, Gr and Vr) in Greenville County data on the weather may be considered to have been fairly certainly represented by the United States Weather Bureau

report for Greenville, and data on pellagra are available for 1917 (chart 77) Table 13 of the Hygienic Laboratory report enables a comparison with available data on the weather of the seasonal incidence and seasonal prevalence of pellagra in 1918 for six villages in the Green-

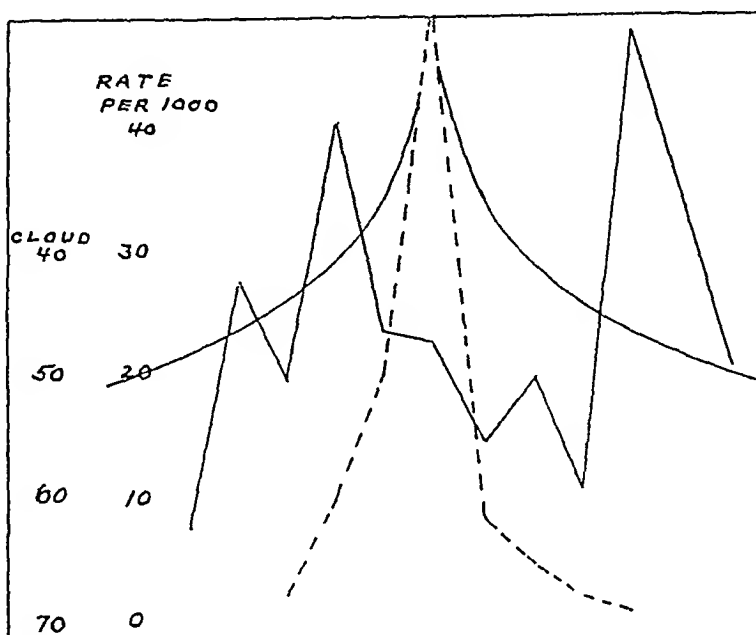


Chart 71—The continuous line indicates the average cloudiness at Greenville in 1917, the broken line, the monthly incidence of pellagra in one village in the area of Greenville in 1917

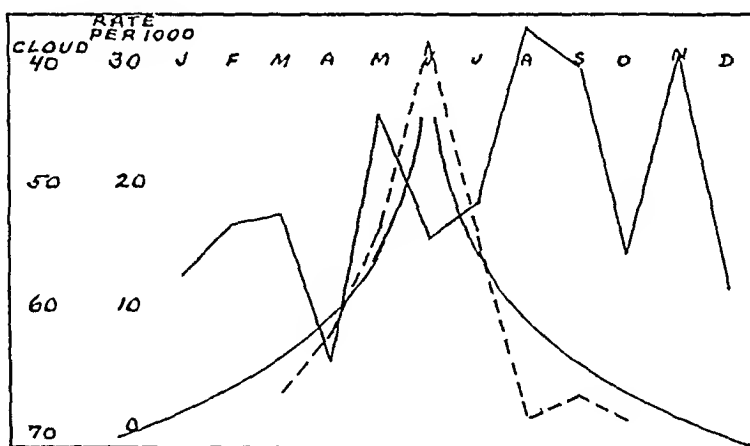


Chart 72—The continuous line indicates the average cloudiness at Greenville in 1918, the broken line, the monthly incidence of pellagra in one village in the area of Greenville in 1918

ville area (chart 78) The incidence of pellagra in 1917 for seventeen villages in the area of Greenville, though not in Greenville County, and condition of the weather prevailing in Greenville at that time are represented in chart 79

Examination of these charts shows no tendency for the peak of pellagra to precede the peak of sunshine. The peak of pellagra is more prone to fall in June and that of sunshine in April (charts 71, 76, 77 and 79). At In, in 1920 (Hygienic Laboratory report,⁴⁵ table 33), there were 5 cases in May and only 4 in June, though the percentage

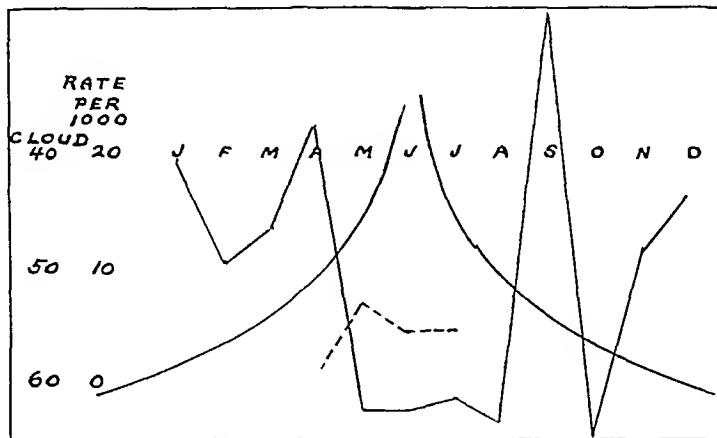


Chart 73—The continuous line indicates the average cloudiness at Greenville in 1919, the broken line, the monthly incidence of pellagra in one village in the area of Greenville in 1919

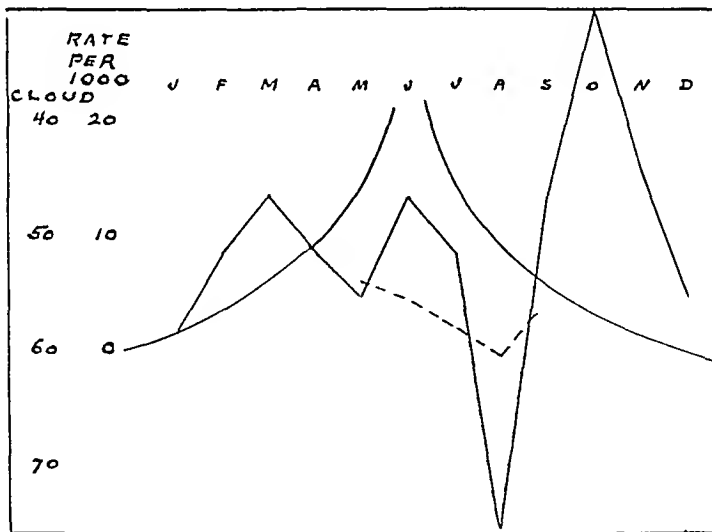


Chart 74—The continuous line indicates the average cloudiness at Greenville in 1920, the broken line, the monthly incidence of pellagra in one village in the area of Greenville in 1920

of sunshine in June was slightly higher than that in May, but the sunshine of March equaled that of June (chart 74), this is obviously negligible. When the peak of pellagra occurred in May (charts 73, 74 and 75), the peak of sunshine occurred in April or March

The clinical progress of the disease is generally similar to the curve of incidence—spring onset, summer exacerbation and improvement in the fall and winter. Any study of the clinical state, metabolism or effect of therapy should therefore take into account the season. Sullivan, Stanton and Dawson's⁹⁷ observations covered the period from July 13 to Oct 11, 1917.

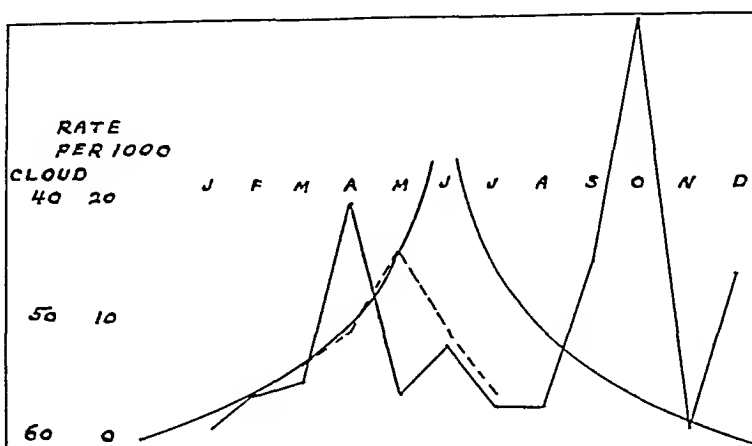


Chart 75—The continuous line indicates the average cloudiness at Greenville in 1921, the broken line, the monthly incidence of pellagra in one village in the area of Greenville in 1921.

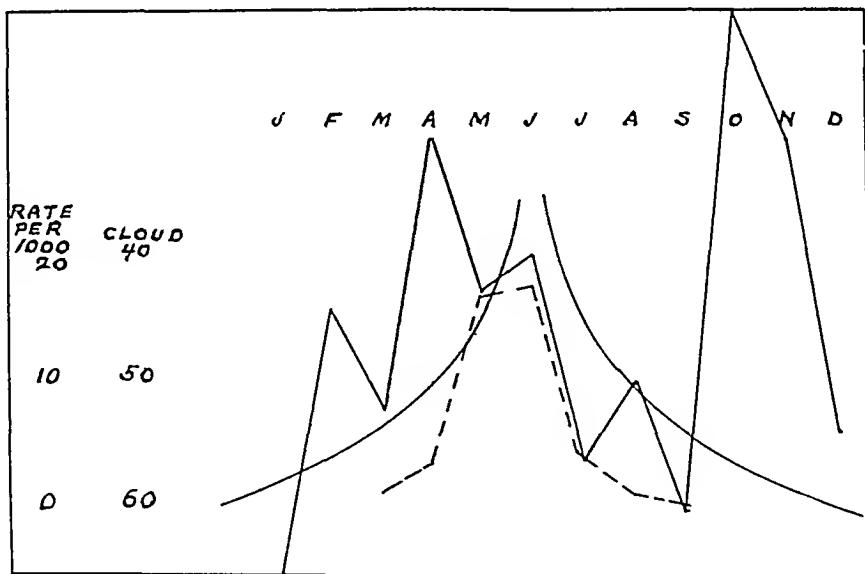


Chart 76—The continuous line indicates the average cloudiness at Columbia in 1917, the broken line, the monthly incidence of pellagra in two villages in the area of Columbia in 1917.

The investigators from the Hygienic Laboratory found that the seasonal prevalence differed from the seasonal incidence only in a lag of time of about two weeks. They stated:

This brings out concretely what has long been recognized clinically, namely, that cases of pellagra "normally" tend to get well in the fall with the advent of

cool weather This old and very striking clinical observation gave rise to the idea that in some way the cooler temperature in itself had a beneficial effect In reality, however, the decline in the season of prevalence, even allowing for the limitations of our data, sets in before the advent of cool weather, so that this can hardly be the real explanation of the phenomenon The similarity of the curve of prevalence to that of incidence naturally suggests that the factors, or some of them, operating to limit the season of incidence also operate to cut short the attack

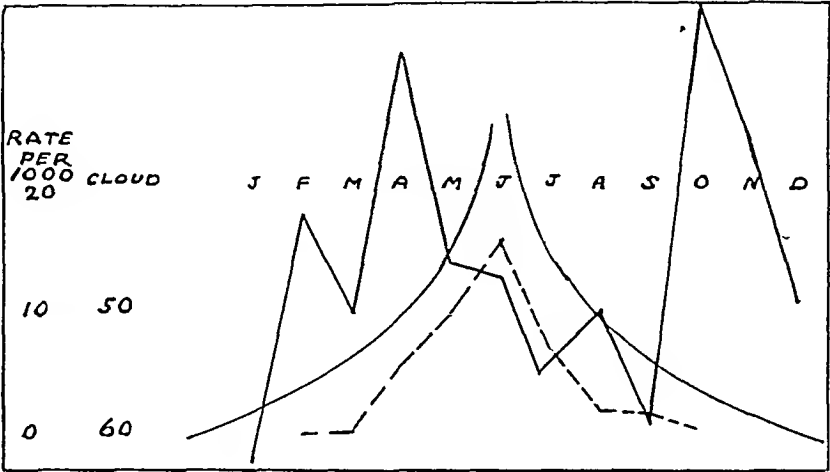


Chart 77—The continuous line indicates the average cloudiness at Greenville in 1917, the broken line, the monthly incidence of pellagra in five villages in Greenville County, 1917

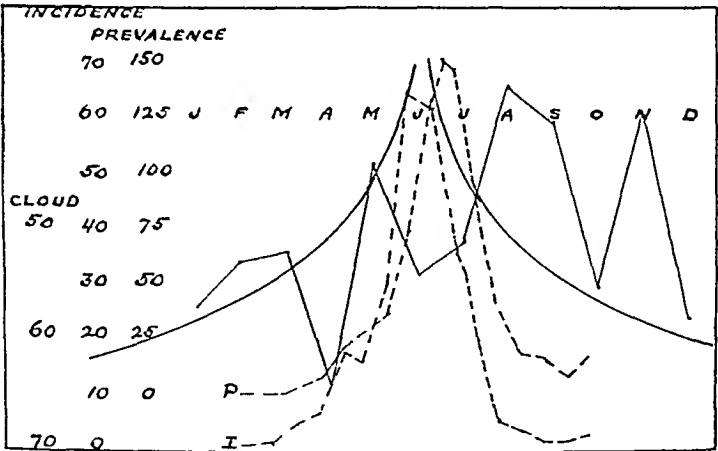


Chart 78—The continuous line indicates the average cloudiness at Greenville in 1918, curve I, the incidence of pellagra in 1918, P, the prevalence of pellagra in 1918, in six villages in the area of Greenville

Here again there appears to be another set of parallels to the curve of the air filter and possibly that of the basal metabolism reversed, culminating in the "normal" tendency to get well in the fall Though the decline of the season of prevalence sets in before the advent of cool weather, it does not set in before the advent of a decline of the sun toward the south

That the investigators from the Hygienic Laboratory did not consider the matter closed with their report is shown by the following discussion

Of the factors suggested as probably concerned in cutting short the season of incidence, the normal seasonal modification in food supply occurring in the summer would seem to be the only one that reasonably can be suggested as capable of operating in such a way as to limit the duration of the attack—that is, of prevalence. *A priori*, this factor would seem entirely adequate to explain the normally self-limiting character of the attack. But whether it actually operates in the manner here suggested, as seems to us most probable, or whether some other factor or factors alone or in cooperation with the seasonal modification in diet are concerned in the explanation of the phenomenon under consideration remain for further study to determine

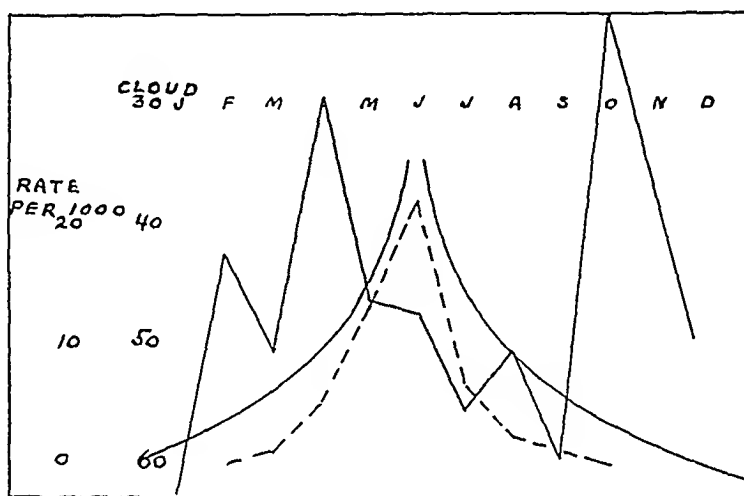


Chart 79—The continuous line indicates the average cloudiness in Greenville in 1917, the broken line, the monthly incidence of pellagra in seventeen villages in the area of Greenville in 1917

VARIATIONS IN THE ANNUAL INCIDENCE OF PELLAGRA WITHIN THE PELLAGRA BELT

In the foregoing discussion of the seasonal incidence of pellagra, the positive influence of varying intensities of sunlight has been considered, without reference to the principle suggested by Laurens as to the effect of deviation from the usual radiant energy. Certain features of pellagra will be considered, with the idea in mind of a positive effect of the ratio between exposure to the solar rays in winter and summer. Stated differently, the tentative assumption is that the solar radiation available in winter by reason of an absence of cloudiness constitutes for the population concerned a standard of "usual radiant energy" which acts as a unit of exposure to which the population has for the time being become accustomed, and deviation from which as the sun approaches the summer solstice tends to produce pellagra. If the intensity of the

summer rays is considered as constant by ignoring summer cloudiness,^{*} increased cloudiness in winter and increased exposure to solar rays in summer, as in the planting of certain crops, would tend to have a positive pellagra-producing effect

The state (and sometimes the county) is the available unit for data concerning the incidence of pellagra. Variations in the annual incidence will therefore be considered with reference to these units, and the apparent influence of the factors winter cloudiness and the planting of crops, together with a factor to be defined later as the delayed incidence or momentum, will be examined

First, however, reference will be made to the relationship between winter cloudiness and the average basal metabolism in a limited set of observations (table 19)

TABLE 19—*Observations at Richmond, Va*

	1927	1928
Low basal metabolic rate for the year	(July) —10.8	(Sept) —8.49
Average for summer months		
June	—6.88	—7.95
July	—10.80	—5.57
August	—7.46	—2.20
Average	—8.38	—5.24
Winter cloud	62	46

The ratios derived from table 19 show, if anything, a depressant effect of increased winter cloudiness (1927) on the average basal metabolism for the following summer months

Chart 80 shows the ratio of the winter cloudiness of 1928 to that of 1927, and the ratio of the pellagra in 1928 to that in 1927 for the states in which pellagra is reportable. Georgia was the only state in which the winter cloudiness of 1928 exceeded that of 1927, but in six states (Virginia, Mississippi, South Carolina, Alabama, Louisiana and Georgia) the ratio of the incidence of pellagra was greater than 1. It follows, therefore, that in general there was a greater incidence of pellagra in 1928 than in 1927, in spite of a generally clearer winter. This general tendency will be referred to later in connection with the delayed onset or momentum. For the present, it is noted that Tennessee, the

* By reason of the lack of solar radiation, a sensitizing feature may well be more significant than the intensity of the summer rays. The mass of the atmospheric filter is not greatly influenced by the angle at the sun's maximum altitude at 40° and 34° latitude, respectively (1.3 miles), but is greatly influenced by the minimal seasonal angle at these latitudes, respectively (18.85 miles). There seems to be little difference between the sun's erythematous power as measured by the air mass penetrated, at Philadelphia (40°) and Wilmington, N. C. (34°), but at Wilmington (34°) and Tampa (28°) there is a difference of 11.3 miles (93.2 miles less 81.9 miles)

state with the lowest ratio of winter cloudiness, did not show an increase, but a fall, in the incidence of pellagra, and that of the four states with the lowest ratio of winter cloudiness (Tennessee, Oklahoma, Virginia and Arkansas), none showed an increase and all, except Virginia, showed a decrease of pellagra in 1928 as compared with 1927

With reference to Virginia, in chart 81 it is obvious that while all sections of the state showed approximately the same decreased ratio of 1928 to 1927 winter cloudiness, the rise in the incidence of pellagra was limited to two sections in which 95.4 per cent of the tobacco crop was planted, that these sections showed an increase in the planting of

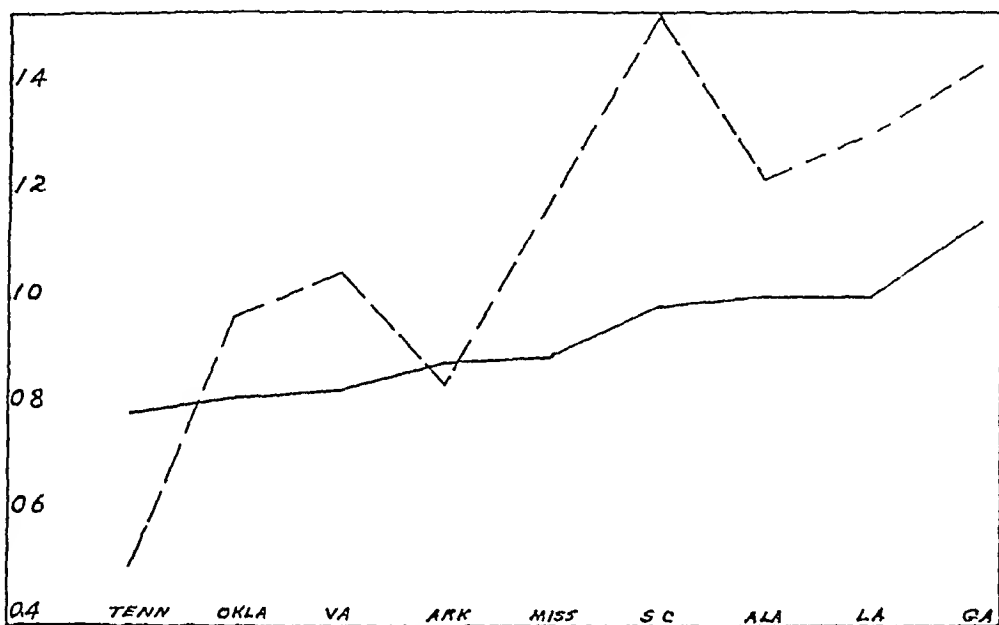


Chart 80—Nine states The continuous line indicates the ratio of winter cloudiness, 1928/1927, the broken line, the ratio of the incidence of pellagra, 1928/1927

tobacco in 1928, and that the increase in pellagra in these sections, respectively, was proportional to the increase in the planting of tobacco

Charts 25 and 82 show the distribution of pellagra and the distribution of tobacco and cotton acreage, respectively, in Virginia in 1927. Wise County (in the southwest) is relatively densely populated and is strikingly low as compared with the other counties of Virginia in the ratio of food and feed raised to the needs of the population.⁴⁸

The remaining five states shown in chart 80 (Mississippi, South Carolina, Alabama, Louisiana and Georgia) showed increased ratios of pellagra in general agreement (except for South Carolina) with the relatively increasing ratios of winter cloudiness. The significance of these comparisons will possibly be increased in view of further analysis to be made of the factors under consideration.

Chart 24 suggests that unusual conditions of the weather, such as the cloudiness in February, 1927, over the area of the southern part of the United States generally, may have peculiar significance. The correlation between the winter cloudiness for 1926 and 1927 and pellagra for these two years is less close than the correlation between the cloudiness in February and pellagra for the same periods.

The predominantly rural character of pellagra (chart 126) suggests that if the duration of exposure to solar rays of relatively high intensity is a factor in the etiology of the disease, the planting of cotton and tobacco is of especial interest because of their importance as major crops in the pellagra belt and because the crops are planted in a relatively

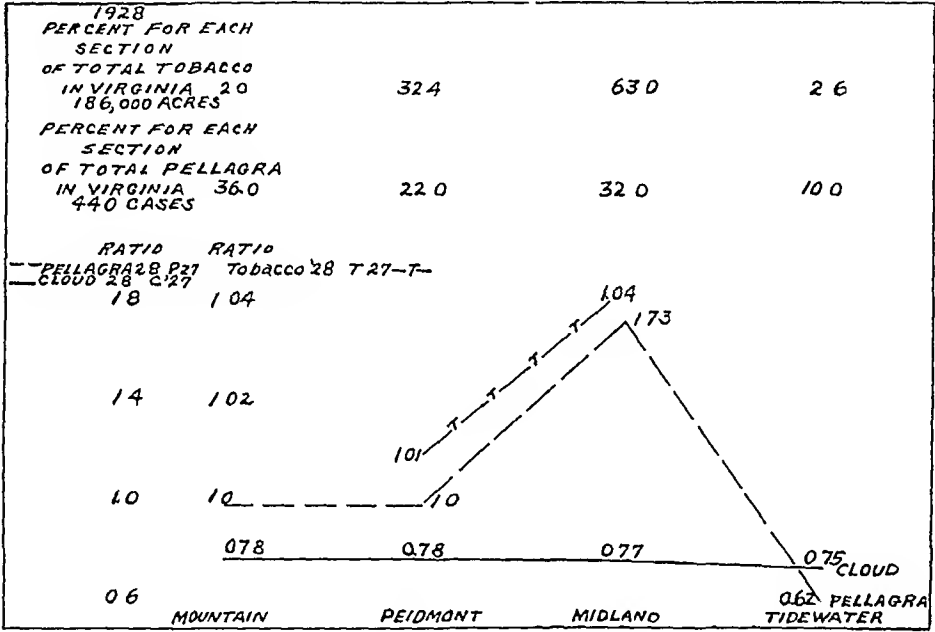


Chart 81—Virginia. The continuous line indicates the ratio of winter cloudiness, 1928/1927, the broken line, the ratio of the incidence of pellagra, 1928/1927, the dash T line, the ratio of tobacco acreage, 1928/1927.

great intensity of solar rays (near the summer solstice) *. However, it should also be noted that these crops probably represent the extreme of the tenantry (economic) factor emphasized by Goldberger and his associates.

If the number of persons required to plant an acre of cotton (one person to five or six acres—Vance), the intensity of the solar rays during the planting of cotton and the dietary characteristics of the popu-

* For comparison with the time of planting these crops in North Carolina with the time of planting and harvesting other crops, reference should be made to the Farm Forecaster, North Carolina, 1928-1929, p. 26, and to Phillips (reference 78).

lation planting the cotton are taken as constant, an acre of cotton may be considered a unit of pellagra-producing factors, as is shown roughly for Mississippi in charts 96 to 101, and a comparison of the incidence of pellagra in relation to the exposure during the previous winter may be regarded as an experiment on a grand scale, the individual characteristics of metabolism being taken care of in an average of the large number of persons employed

Delayed Incidence or Momentum—Whatever the conditions favorable to a high incidence of pellagra may be, it seems reasonable to assume that conditions operating broadly to produce a high incidence in any given year would tend to affect an indefinite number of persons

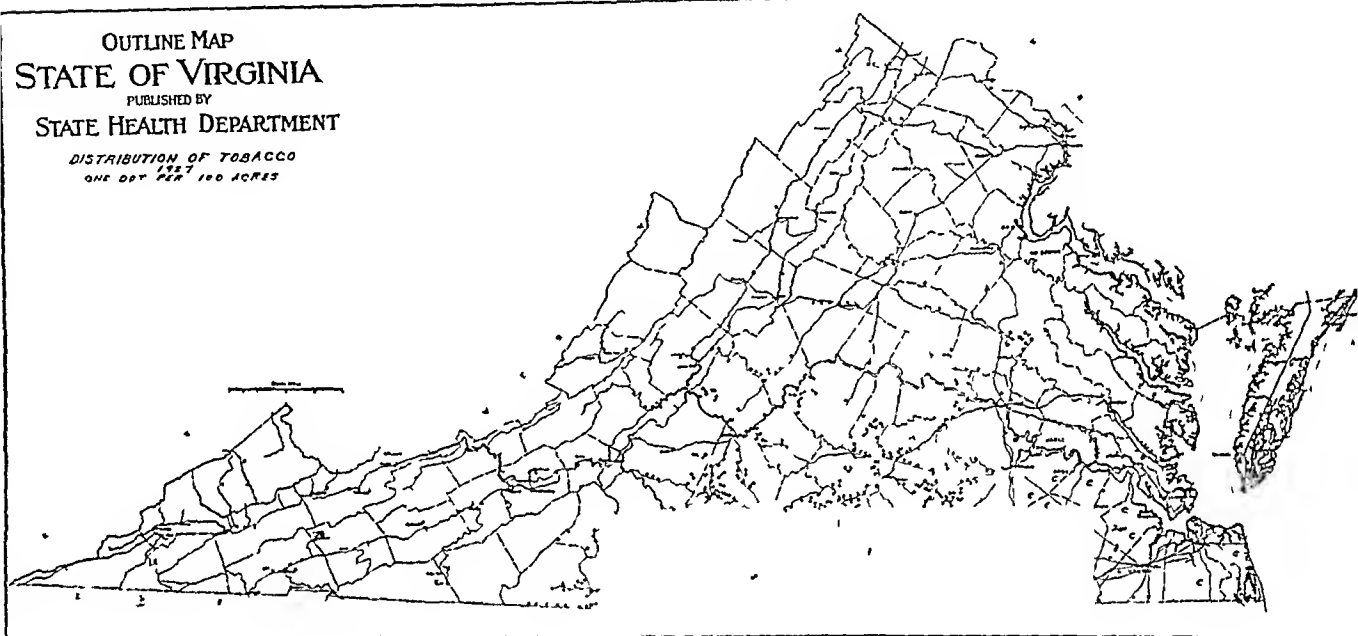


Chart 82—Virginia, 1927 The dots show the distribution of tobacco acreage (divided by 100), c shows the distribution of cotton acreage (divided by 1,000)

who, whether the disease did or did not develop in them during the current year, would be somewhat more liable to the disease the following year than would have been the case had the conditions of the current year been less favorable to a high incidence. In other words, an increased incidence, for example, in 1927 as compared with that in 1926, might be expected to tend to an increase in 1928 in the absence of a definite reduction in the pellagra-producing factors. This assumed tendency may be referred to as a delayed incidence or momentum.

The relative incidence in 1927 was actually and generally high in comparison with that in 1926 (chart 24), and thus conditions favorable to the further increase in 1928 were probably created. Such may also be the significance of the observation of the Hygienic Laboratory,¹⁵ that "recurrent attacks probably tend to appear somewhat earlier in the

year than do initial attacks" (p 33) However, if the supposed "delayed incidence" is real, the data point to the fact that the delay and the subsequent development of the disease are limited and defined by the same curve as the incidence of new cases as a whole and of recurrent cases, namely, the curve of the an filter

It is hardly open to question that any tendency to error through the listing of recurrent cases as new cases would tend to be exaggerated by a high incidence during the previous year and thus add to a seeming momentum

The idea of a delayed incidence may be illustrated by the fact that a seed that is sown one year may spring up the following year Wood¹²⁰ referred to pre-pellagrous symptoms that made their first appearance about Christmas time, suggesting a premonitory hint of a delayed incidence

The investigators from the Hygienic Laboratory⁴⁵ referred to a possible "exhaustion of the human material of pellagrous potentiality"

TABLE 20—Mississippi

	Jan	Feb	March	April	May	Total	Nov	Dec
1926	210	245	353	652	1,178	7,180	314	213
1927	217	257	394	685	1,100*	11,570	638†	313†
1928	355†	349†	549	1,029	1,865	13,810	514	279

* Estimated

† There was not an indication of "exhaustion of human material," but an indication of susceptibility of population and increased potentiality for the succeeding year

(p 34) It is possible that Washington County, Mississippi, represents an instance of this exhaustion (see table 21) The notion involved in "delayed incidence" is the opposite It does not seem inherently contradictory to suppose that high sunshine in the winter might result in an increased incidence of pellagra during the winter months and at the same time tend to offset the development of the disease during the following summer

The tendency to a delayed incidence may be illustrated in the figures given in table 20 for Mississippi

Statistically, there is a valid objection to considering along with supposed etiologic factors one expression of the incidence of pellagra when the effect under consideration is another expression of this incidence This objection is regarded as somewhat less valid in view of the tendency for the incidence of pellagra to approach zero in the winter

In North Carolina, pellagra was not made a reportable disease until 1929, however, the curve of the death rate in the state for several years is shown in chart 83 There is a decidedly upward trend after 1923 The trend of the curve representing winter cloudiness, cotton and

tobacco, when reduced to a common scale, is also upward until 1927 (chart 84). In 1927, the death rate for pellagra showed a further rise, though there was a sharp reduction in the planting of cotton. Winter cloudiness and the planting of tobacco, however, were in excess in 1926. In 1928, the death rate for pellagra still further increased, cotton and tobacco acreage increased over that of 1927, but the winter cloudiness showed a sharp decline. It is possible that the increased death rate for pellagra reflected the history of pellagra of the preceding several years (momentum). Further data are necessary before the relative influence of pellagra-producing and pellagra-reducing factors can be appraised. The scales used in chart 84 are purely arbitrary and do not furnish a basis for a comparison of values, except in trends.

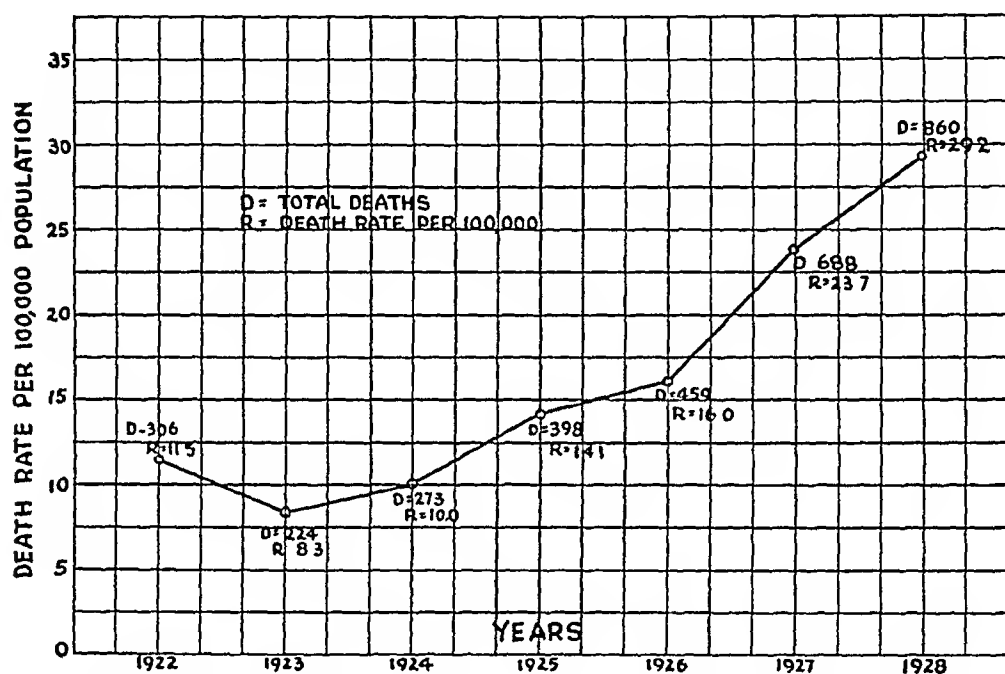


Chart 83—Death rates from pellagra in North Carolina, from 1922 to 1928
(From the North Carolina State Board of Health)

If in any year in any state an increased incidence of pellagra (assuming reliable data) and a decline in winter cloudiness, cotton, tobacco and momentum are noted, it is obvious that the etiologic factors of pellagra are not comprehended in these influences. However, the evidence that has been adduced by Goldberger and others in favor of a deficiency of food and an economic cause of pellagra has been employed by them with scientific caution as explanatory of certain features of the incidence of the disease (Hygienic Laboratory Bulletin,⁴⁵ pp 45-64) and obviously is available for consideration in connection with any other supposed etiologic factor. These authors⁴⁵ stated that

It seems reasonable to infer, therefore, that the year-to-year fluctuations in pellagra incidence in endemic localities are bound up with year-to-year fluctuations

in economic conditions—that is, with conditions that influence the ability of a certain section of the population to procure an adequate diet, particularly at a certain season, the late winter and early spring of the year. We believe we have here in a concrete, definite and scientific form, based on intensive study, the explanation, or a very important part of the explanation, of the long recognized phenomenon of year-to-year fluctuations in incidence of endemic pellagra (p 60) *

Charts 85, 86 and 87 show the distribution of deaths from pellagra and of cotton and tobacco acreage, respectively, in North Carolina in 1928. For comparison, charts 88, 89 and 90 show the distribution of other major crops in this state in the same year.

Charts 91 and 92 show the distribution of pellagra and of cotton and tobacco acreage, respectively, in South Carolina for 1927. Chart

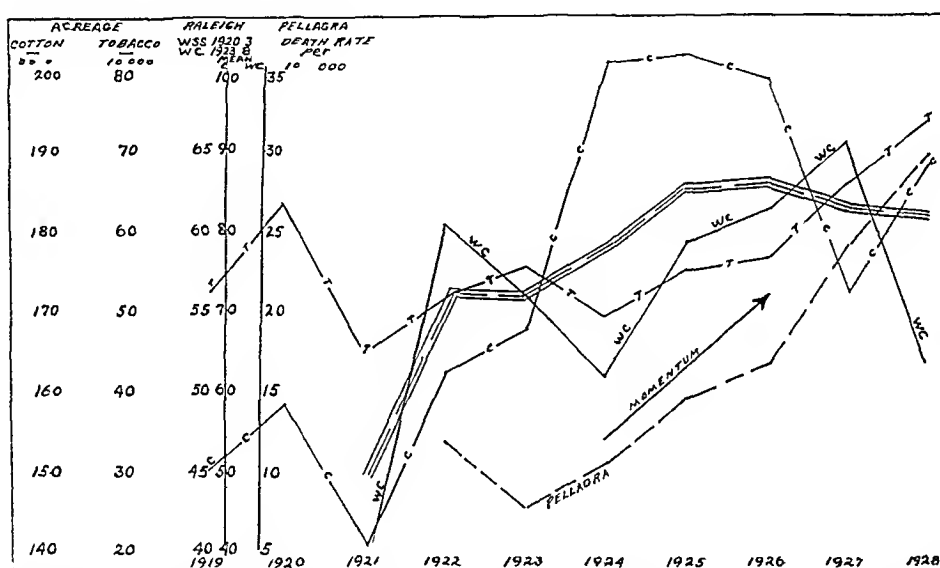


Chart 84—North Carolina. Curve *c* indicates the cotton acreage, curve *T*, the tobacco acreage, and curve *WC*, the winter sunshine from 1921 to 1923, and winter cloudiness, from 1924 to 1928, at Raleigh. The triple line indicates the mean cotton acreage, tobacco acreage and winter cloudiness, the broken line, the death rate from pellagra per hundred thousand.

91 also shows the approximate location of the twenty-four villages studied in the Hygienic Laboratory report.

Though not necessarily a contradiction, it is nevertheless difficult to apply this principle to the decrease in pellagra in certain European countries following the World War. In the League of Nations Health Reports a statement is made to the effect that the decrease in pellagra in Roumania after the war was expected to be permanent, but it was found otherwise. In contrast is McCollum's statement: "Marked deficiency of protein in the diet over a considerable period, as when the population is at war or approaching famine conditions, and is forced to subsist on a diet of cabbage, lettuce and other green foods, has been observed to cause endemic dropsy" (reference 72). This, however, is not the deficiency described by Goldberger.

The annual incidence of pellagra in 1926, 1927 and 1928, in Arkansas and Mississippi, is of special interest. The incidence will be considered in connection with the data available for each, which differ in some respects.

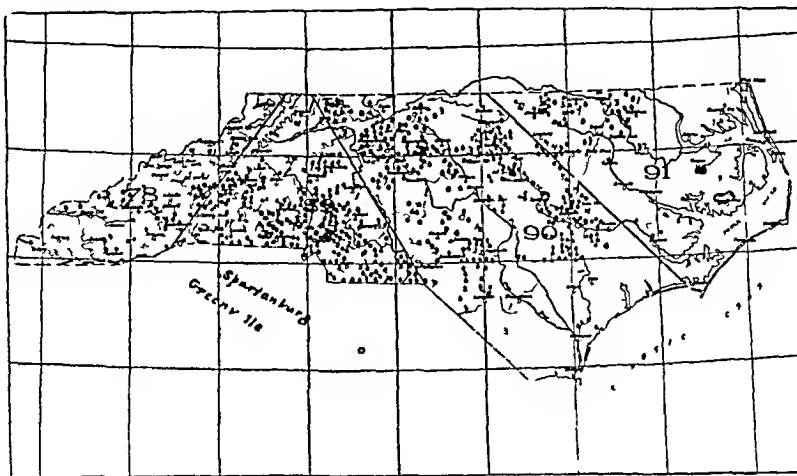


Chart 85—Distribution of deaths from pellagra in North Carolina in 1928
(From the North Carolina State Board of Health)

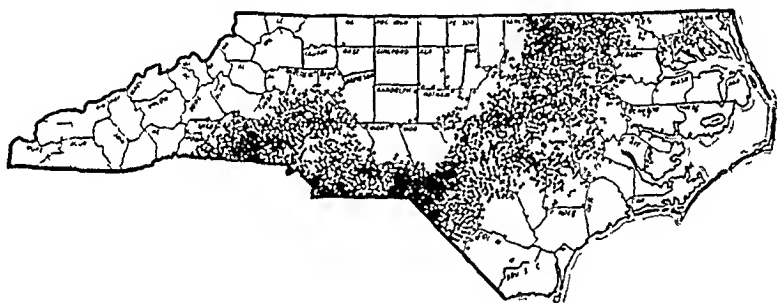


Chart 86—North Carolina, 1928. Distribution of the cotton acreage. The value of the 1928 crop of cotton lint is represented by one dot to each \$25,000.

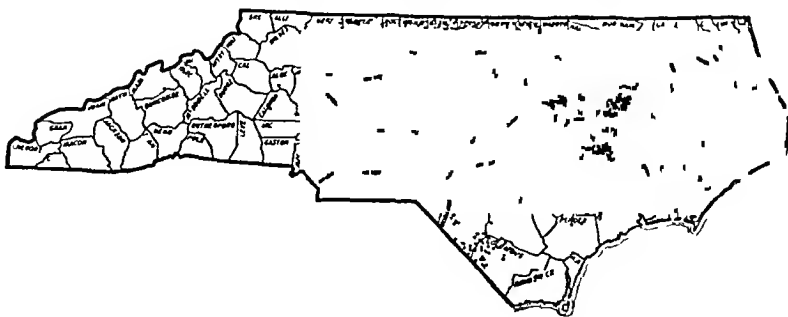


Chart 87—North Carolina, 1928. Distribution of the tobacco acreage. The value of the 1928 crop of tobacco is represented by one dot to each \$50,000.

In Arkansas, in each of the three sections of the state, western, middle and eastern (charts 93, 94 and 95), the winter cloudiness of 1927 exceeded that of 1926 and 1928, and conversely the cotton acreage was

reduced in 1927⁴ The net result apparently attributable to these factors was a rise in the incidence of pellagra in 1927 above that of 1926 or 1928, roughly in proportion to the excess of winter cloudiness If the increased incidence of pellagra in 1927 is considered as a factor of momentum resulting in a delayed incidence, its effect is seen in the failure

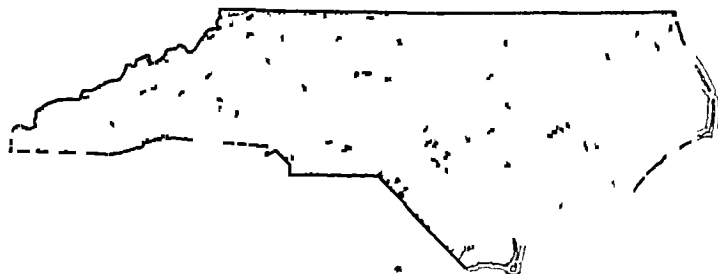


Chart 88—North Carolina, 1928 Distribution of the corn acreage The value of the 1928 crop of corn (gram) is represented by one dot to each \$10,000

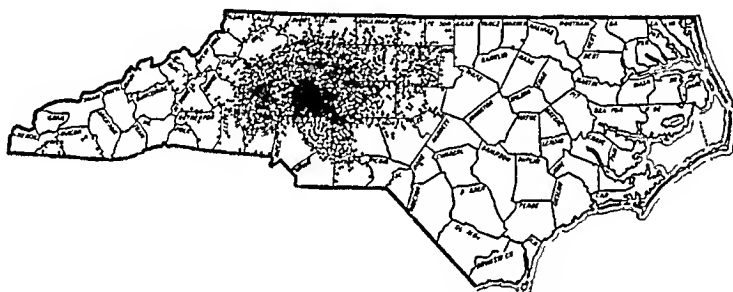


Chart 89—North Carolina, 1928 Distribution of the wheat acreage The value of the 1928 crop of wheat is represented by one dot to each \$5,000

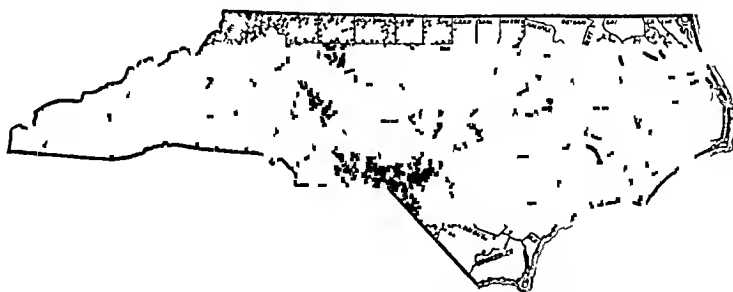


Chart 90—North Carolina 1928 Distribution of the oat acreage The value of the 1928 crop of oats (gram) is represented by one dot to each \$1,000

of the incidence of 1928 to fall to levels comparable with those of 1926, though in 1928 an increase in cotton acreage would also have to be considered

Arkansas was part of the flood area of 1927 (American National Red Cross³ United States Department of Agriculture¹⁰⁵ and United States Public Health Reports¹⁰⁹), and the increased incidence of pel-

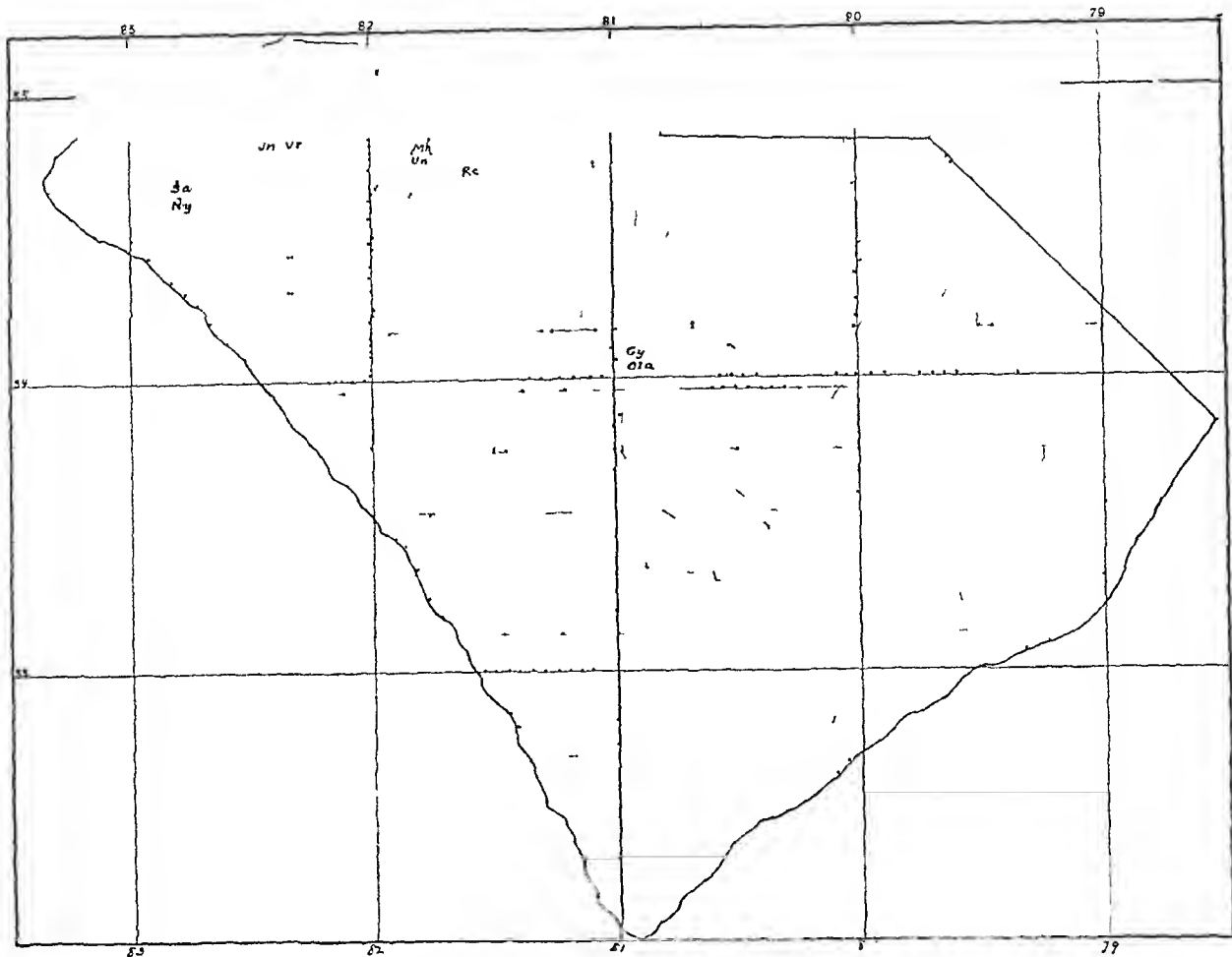


Chart 91—Incidence and distribution of pellagra in South Carolina in 1927 (From the South Carolina State Board of Health) The lettering indicates the approximate location of the villages studied, as reported by the Hygienic Laboratory

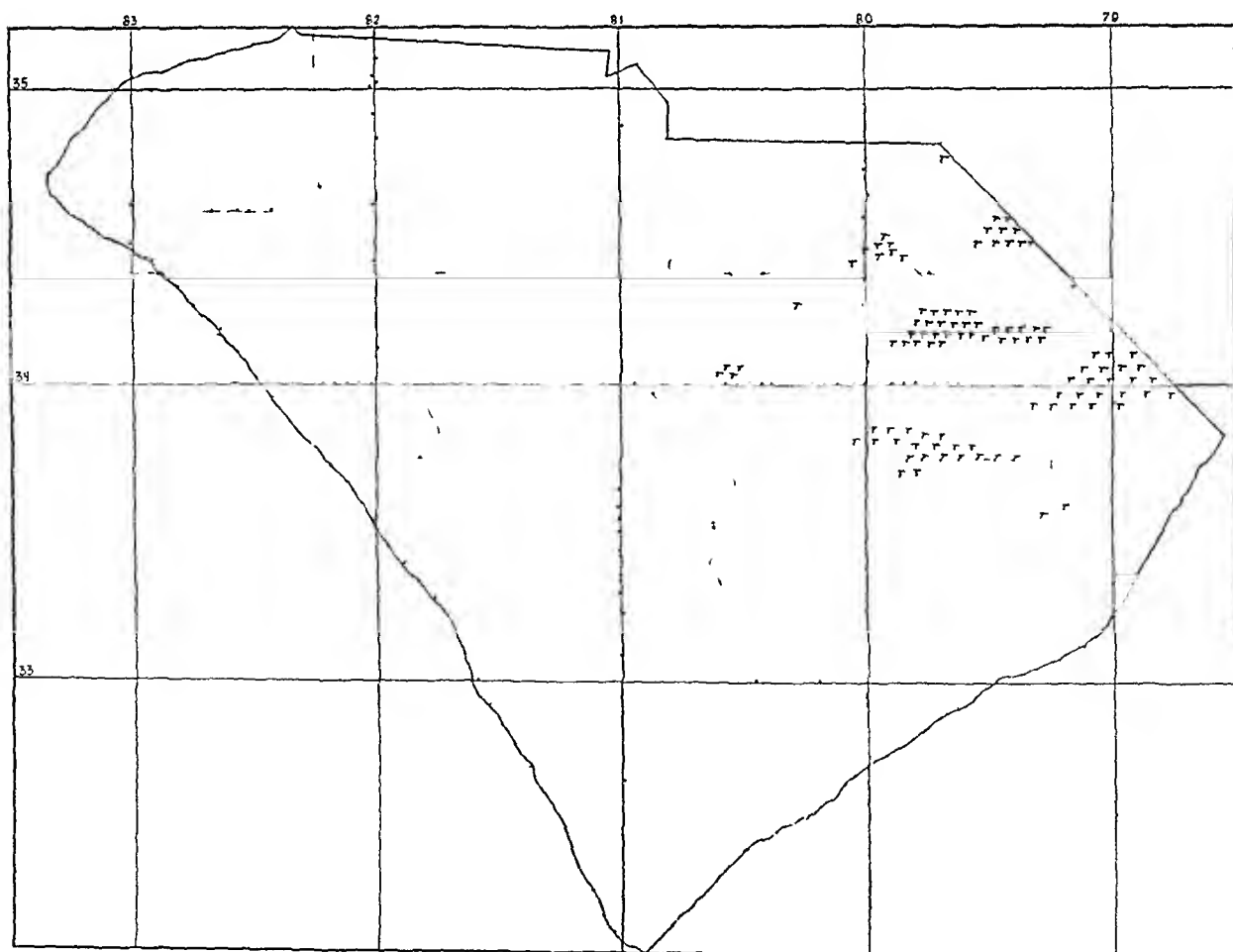


Chart 92—South Carolina, 1927 The dots indicate the distribution of the cotton acreage (divided by 1,000), T, the distribution of the tobacco acreage (divided by 1,000)

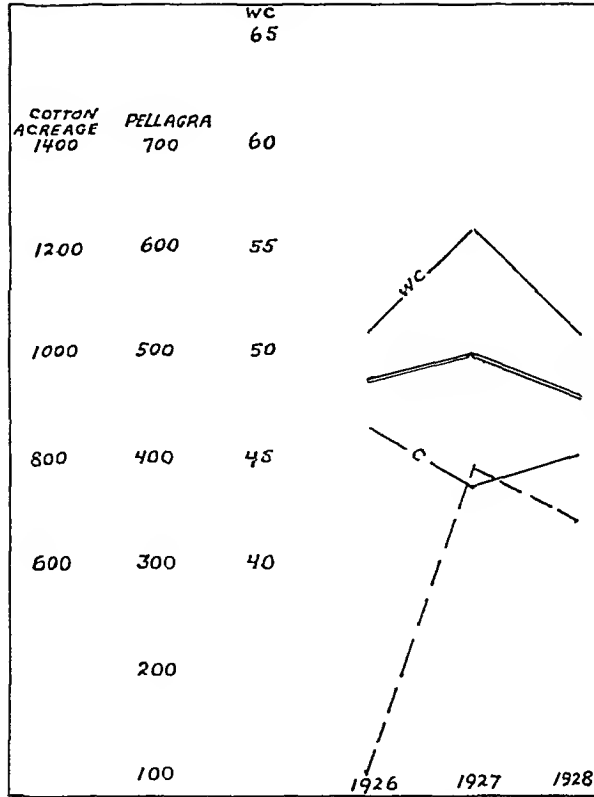


Chart 93—Arkansas, area of Fort Smith Curve *WC* indicates the winter cloudiness, curve *C*, the cotton acreage, the double line, the mean winter cloudiness and cotton acreage, and the broken line, the incidence of pellagra

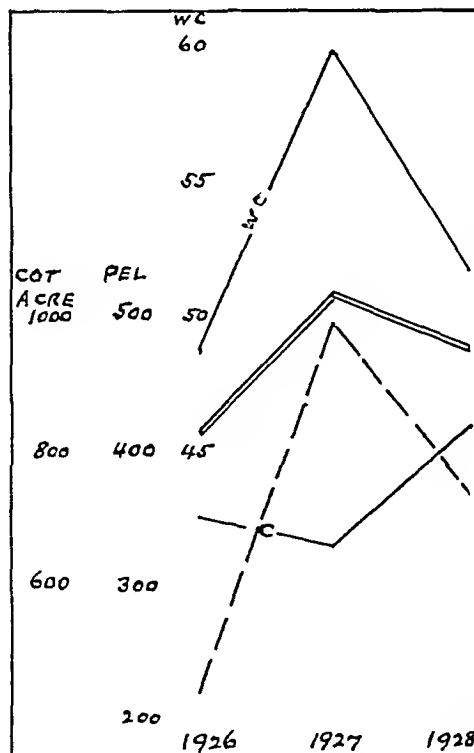


Chart 94—Arkansas, area of Little Rock Curve *WC* indicates the winter cloudiness, curve *C*, the cotton acreage, the double line, the mean winter cloudiness and cotton acreage, and the broken line, the incidence of pellagra

lagra was anticipated by the United States Public Health Service on the basis of a deficiency of food and economic distress. While observation does not disparage the effectiveness of the relief work or disprove the theories on which the relief work among pella-

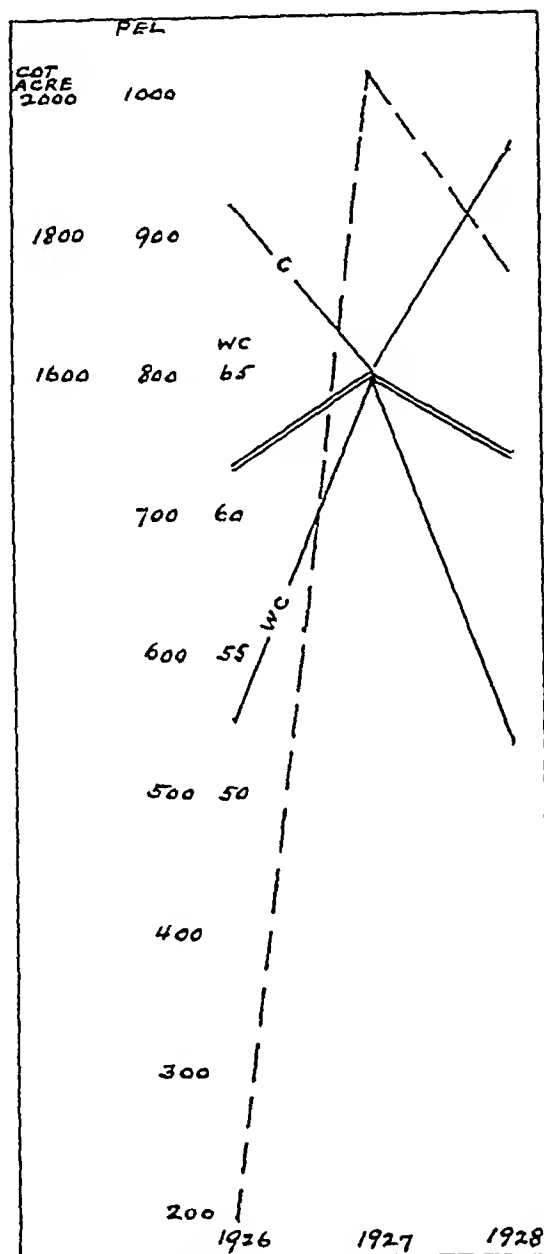


Chart 95—Arkansas, area of Memphis. Curve *WC* indicates the winter cloudiness, curve *C*, the cotton acreage, the double line, the mean winter cloudiness and cotton acreage, and the broken line, the incidence of pellagra.

grins was based, it is of interest to note that Thatcher,⁹⁹ in a study of the conditions in Pulaski County, Arkansas, reported that Dr. Paul L. Day estimated the vitamin B content of the diet in acute cases that developed after the flood, and while the results seemed to show a

deficiency of this and other vitamins both before and after the flood, the deficiency in vitamin B was rather more marked before than after.

The available data for Mississippi are shown in charts 96, 97, 98, 99, 100 and 101. This state was also involved in the flood of 1927. It is to be noted that the scale adopted for the representation of the incidence of pellagra is ten times that of Arkansas. Figures for the cotton acreage by counties are not available for 1926, 1927 and 1928, except for ten counties in the flood area for 1926 and 1927, and these are only approximate.¹⁰⁵ With the use of the United States Census

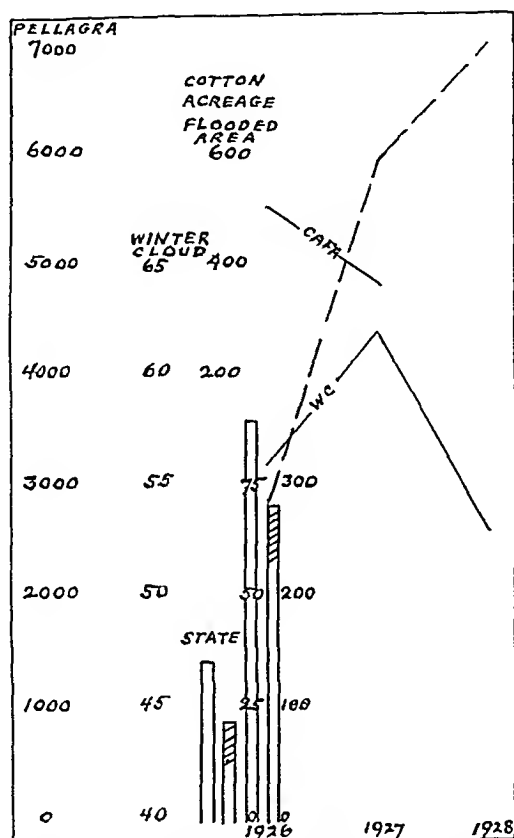


Chart 96—Mississippi, ten flood counties. *CAFA* indicates the cotton acreage in flooded area, curve *WC*, the winter cloudiness, the broken line, the incidence of pellagra, the vertical column, plain, the average cotton acreage per county (divided by 1,000), in 1919, from the United States census, the vertical column, hatched, the average amount of pellagra per county, 1926.

figures for 1920 (for the year 1919), a striking correlation is noted between the cotton acreage in 1919 and the incidence in 1926 of pellagra (vertical shaded columns in the charts).

In regard to the possible influence of winter cloudiness and its apparent influence as compared with "momentum," a somewhat unique opportunity is afforded in this state during these years to note reversed conditions with reference to winter cloudiness in different parts of the

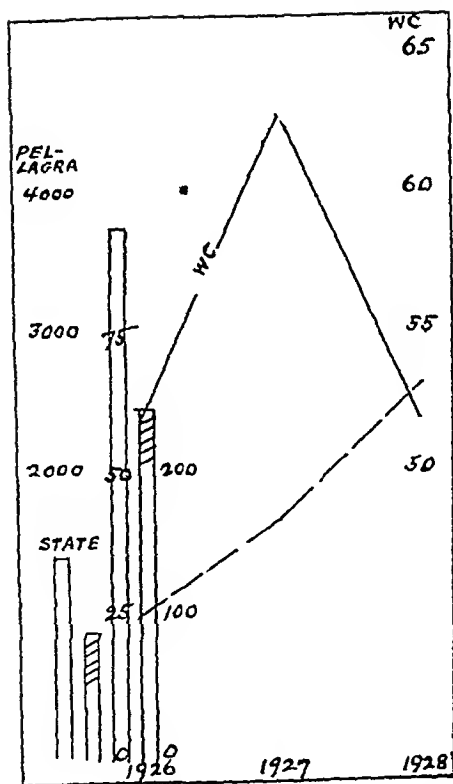


Chart 97—Mississippi, four lesser flood counties, northern Curve *WC* indicates the winter cloudiness, the broken line, the incidence of pellagra, the vertical column, plain, the average cotton acreage per county, 1919, the vertical column, hatched, the average amount of pellagra per county in 1926

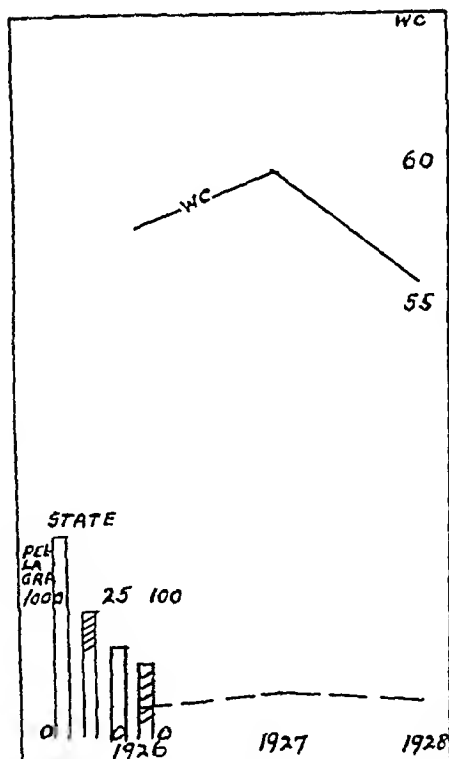


Chart 98—Mississippi, four lesser flood counties, southern Curve *WC* indicates the winter cloudiness, the broken line, the incidence of pellagra, the vertical column, plain, the average cotton acreage per county in 1919, the vertical column, hatched, the average amount of pellagra per county in 1926

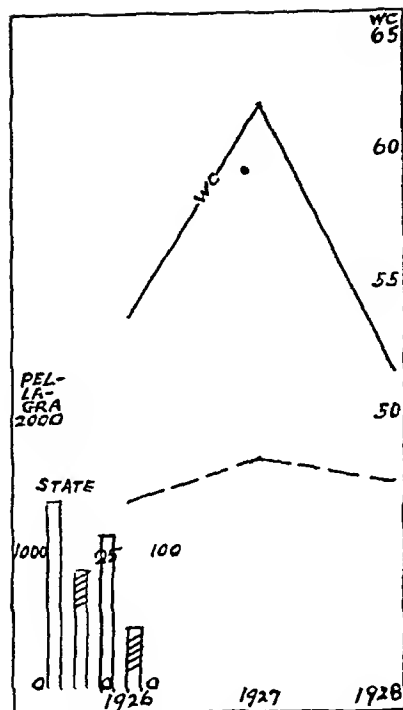


Chart 99—Mississippi, twenty-nine northern counties Curve *WC* indicates the winter cloudiness, the broken line, the incidence of pellagra, the vertical column, plain, the average cotton acreage per county in 1919, the vertical column hatched, the average amount of pellagra per county in 1926

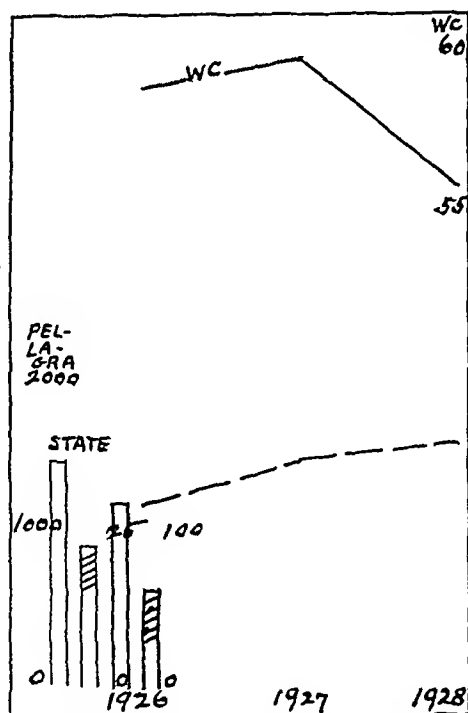


Chart 100—Mississippi, nineteen south central counties Curve *WC* indicates the winter cloudiness, the broken line, the incidence of pellagra, the vertical column, plain, the average cotton acreage per county in 1919, the vertical column, hatched, the average amount of pellagra per county in 1926

state In all sections of the state, except in sixteen southern counties, the winter cloudiness in 1927 was in excess of that in either 1926 or 1928 The area of these sixteen counties was also the only one in which the incidence of pellagra for 1927, as reported, was lower than that for 1926 or 1928 (chart 101) In general, during these three years, the incidence of pellagra conformed to the variation in winter cloudiness in all sections, however, in the fourteen northern counties included in the flood area, the incidence of pellagra for 1928 was higher than that for 1927, whereas winter cloudiness was lower Economic conditions may have been worse in 1928 than in the year of the flood, but this

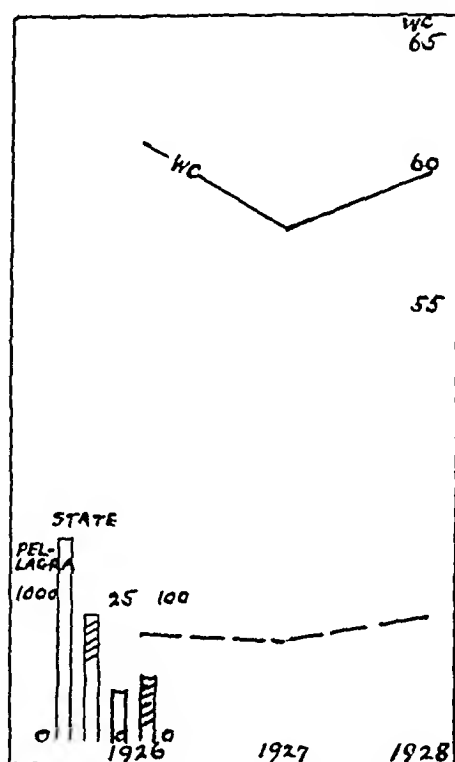


Chart 101—Mississippi, sixteen southern counties Curve *WC* indicates the winter cloudiness, the broken line, the incidence of pellagra, the vertical column, plain, the average cotton acreage per county in 1919, the vertical column, hatched, the average amount of pellagra per county in 1926

would seem improbable On the other hand, it is noticeable that these counties constitute an area of normally large cotton acreage, of high incidence of pellagra for 1926 and of a gross numerical increase in incidence for 1927 (approximately 3,100 and 700 cases, respectively, charts 96 and 97) If the increased incidence of pellagra in 1927 is considered a factor of momentum resulting in a delayed incidence, its effect is seen in the failure of the incidence for 1928 to fall, on the contrary, an actual and marked rise occurred

Chart 102, which includes the ratios of winter cloudiness, cotton acreage in the flooded areas and the incidence of pellagra for 1926

and 1927, for the ten major counties in which the flood occurred, shows for the first seven counties a fairly consistent conformity to the positive influence of winter cloudiness and the planting of cotton on the incidence of pellagra as suggested by previous figures. Of the three other counties, two, Issaquena and Warren, reported only 8 and 59 cases of pellagra, in 1926, respectively, and therefore are hardly suitable for statistical purposes. The great increase of pellagra in Washington County in 1927 may have had some relationship to the figures given in table 21.

Whether or not the figures in table 21 embody an explanation of the relatively high ratio of pellagra in Washington County in 1927 is

TABLE 21—*Incidence of Pellagra in Counties*

County	Population in 1920 in Thousands	Population per Square Mile in 1920	Cotton Acreage in 1919 in Thousands	Crop Acreage Flooded in 1927 in Thousands	Population Affected by the Flood in Thousands	1926 Cotton Acreage Flooded in 1927 in Thousands	1927 Cotton Acreage in Flooded Area in Thousands*	Pellagra per Square Mile, 1907-1911, Inclusive	Pellagra in Whole County, 1926	Pellagra in Whole County, 1927	Pellagra in Whole County, 1928
Bohvar	57	65	215	93	17	75	48	0.081	774	1,167	1,842
Sunflower	46	68	151	92	20	76	58	0.078	582	1,060	1,169
Leflore	37	65	109	36	6	27	19	0.068	408	702	820
Holmes	34	46	78	20	6	15	9	0.071	245	467	451
Sharkey	14	33	42	74	14	55	37	0.040	198	406	470
Humphreys	19	17	56	91	24	72	51	0.057	165	321	574
Yazoo	37	41	76	76	14	55	44	0.037	152	217	215
Washington	51	70	134	189	55	140	108	0.142	265	1,481	1,184
Issaquena	7	18	23	43	8	21	14	0.001	8	52	42
Warren	33	38	22	21	5	14	7	0.001	59	132	163

* This column represents actually the "Acres of flood area expected to be planted in 1927" in other crops than corn and hay, as "an act of Congress specifically prohibits our publishing any report regarding intentions to plant cotton." By comparison of other sets of data on "other crops" and cotton, about 92 per cent of the foregoing figures represented cotton acreage.

not entirely clear. The population affected by the flood was much greater than that in any other county. The flooding of a high percentage of the cropland of this county may have resulted in extreme economic deprivation. Extensive planting of cotton under postflood conditions may have involved labor and exposure to midsummer solar rays in a degree not normal to the planting of cotton. The fact that in the early period, from 1907 to 1911, Washington County had a greater population per square mile and a larger incidence of pellagra per square mile than any other county in this group may be of significance. The failure of this county to show an increased incidence in 1928 also remains unexplained. Figures for the acreage of cotton for the counties of the entire state for 1926, 1927 and 1928 might throw further light on the relative incidence, but these figures have not been available.

Charts 103 and 104 show the distribution of pellagra and cotton, respectively, in Mississippi for 1926 and 1919.

Charts 105 to 126 are presented by way of a summary of the factors that have been discussed as having a possible relation to the annual incidence of pellagra in a given area. Their significance is subject to several important limitations, which will be mentioned, and doubtless to other limitations that will be apparent to expert statisticians. Variations in the scales used in different figures for the same class of data, for example, the incidence of pellagra in Virginia and in Mississippi, limit their significance to the representation of trends rather than of absolute values. Agricultural values for Virginia are

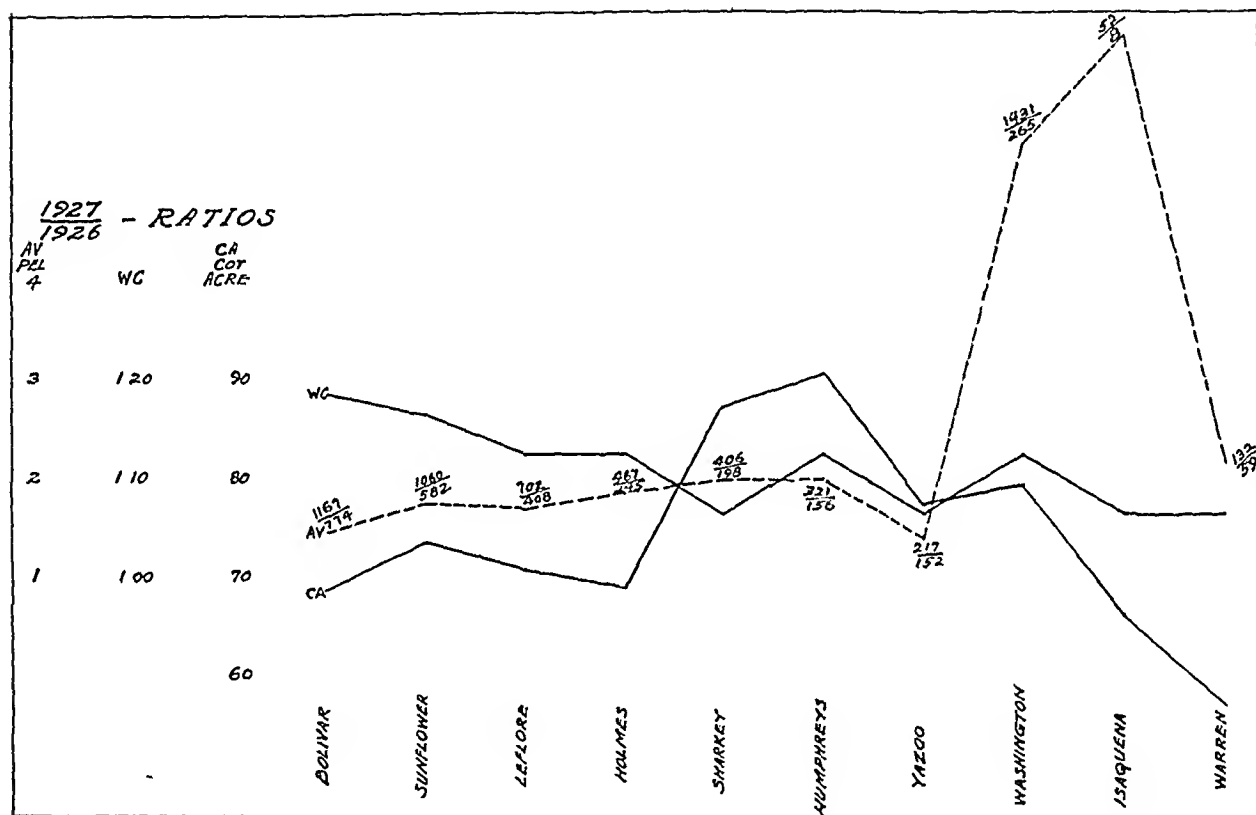


Chart 102 Ten major flood counties of Mississippi in 1927, with ratios of 1927/1926. Curve *WC* indicates the winter cloudiness, curve *CA*, the cotton acreage in the flooded area of each county, the broken line, the incidence of pellagra.

based on tobacco, the relatively small amount of cotton planted being ignored. For South Carolina, the crop of tobacco is ignored, and for Tennessee, the curves pertaining to the value of tobacco are shown, but are not included when means of curves are plotted. Except for Virginia, cotton is the basis of the agricultural values used.

The curve of deaths from pellagra in the United States Registration area (*Z*, chart 126) is probably more nearly in accord with actual conditions than the various curves representing the incidence of pellagra, such as *AV* in chart 126. However, certain of the reports of

the incidence of the disease would appear to have a fairly reliable accuracy in view of the fact that in the Report of the Bureau of Communicable Diseases for June, 1930, in Mississippi, the percentage of physicians reporting is given as 99.18

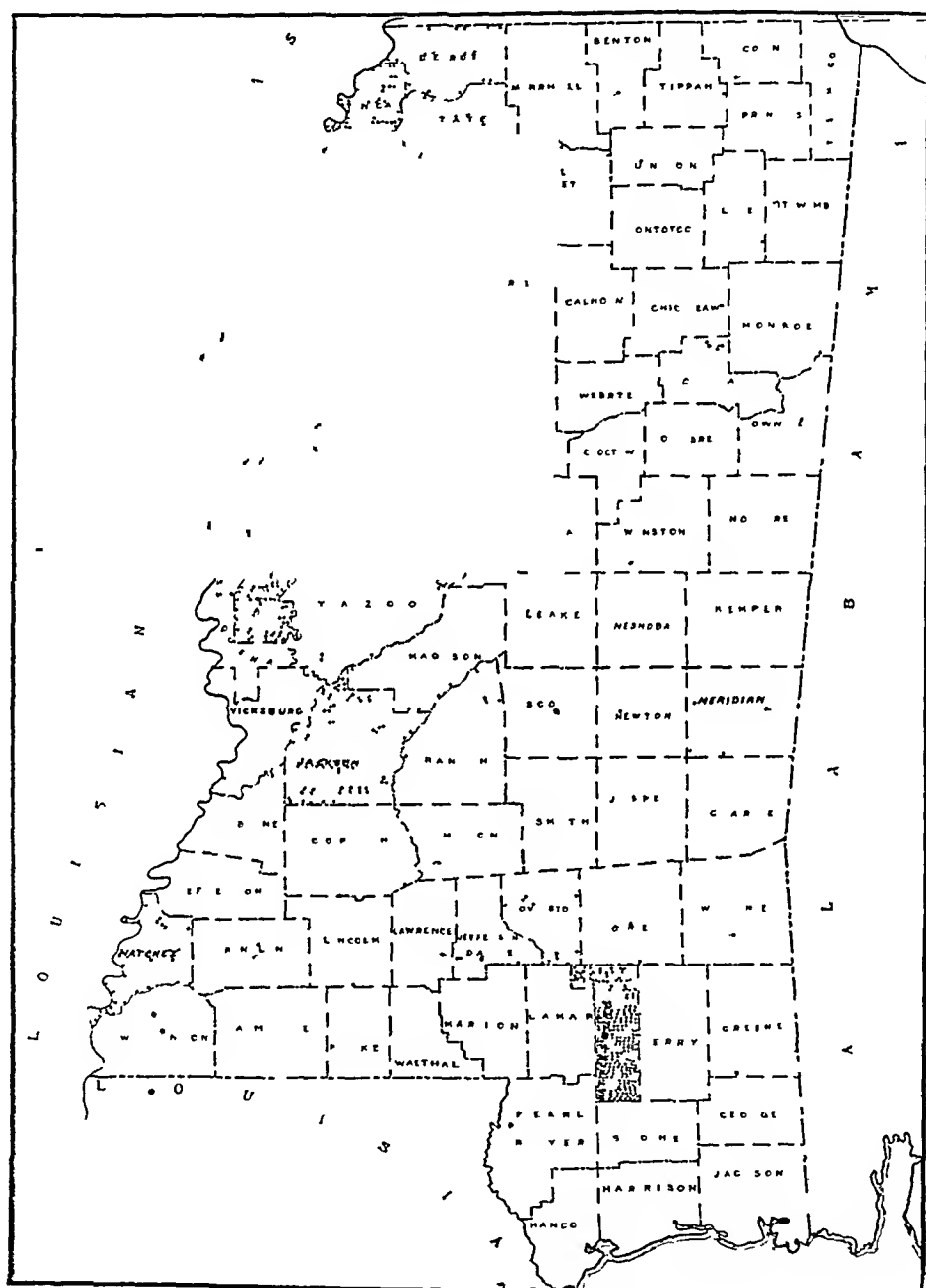


Chart 103—Incidence and distribution of pellagra in Mississippi in 1926
(From the Mississippi State Board of Health)

A primary assumption underlying charts 106 to 125 is that the factors determining the influence of pellagra may vary in different seasons of the year, and with respect to the eighteen charts (charts 106

to 123) for nine states, half of the figures represent the first and half the second six months of the annual cycle. Likewise, charts 124 and 125, showing composite data for four states, represent the first and second half years, respectively.

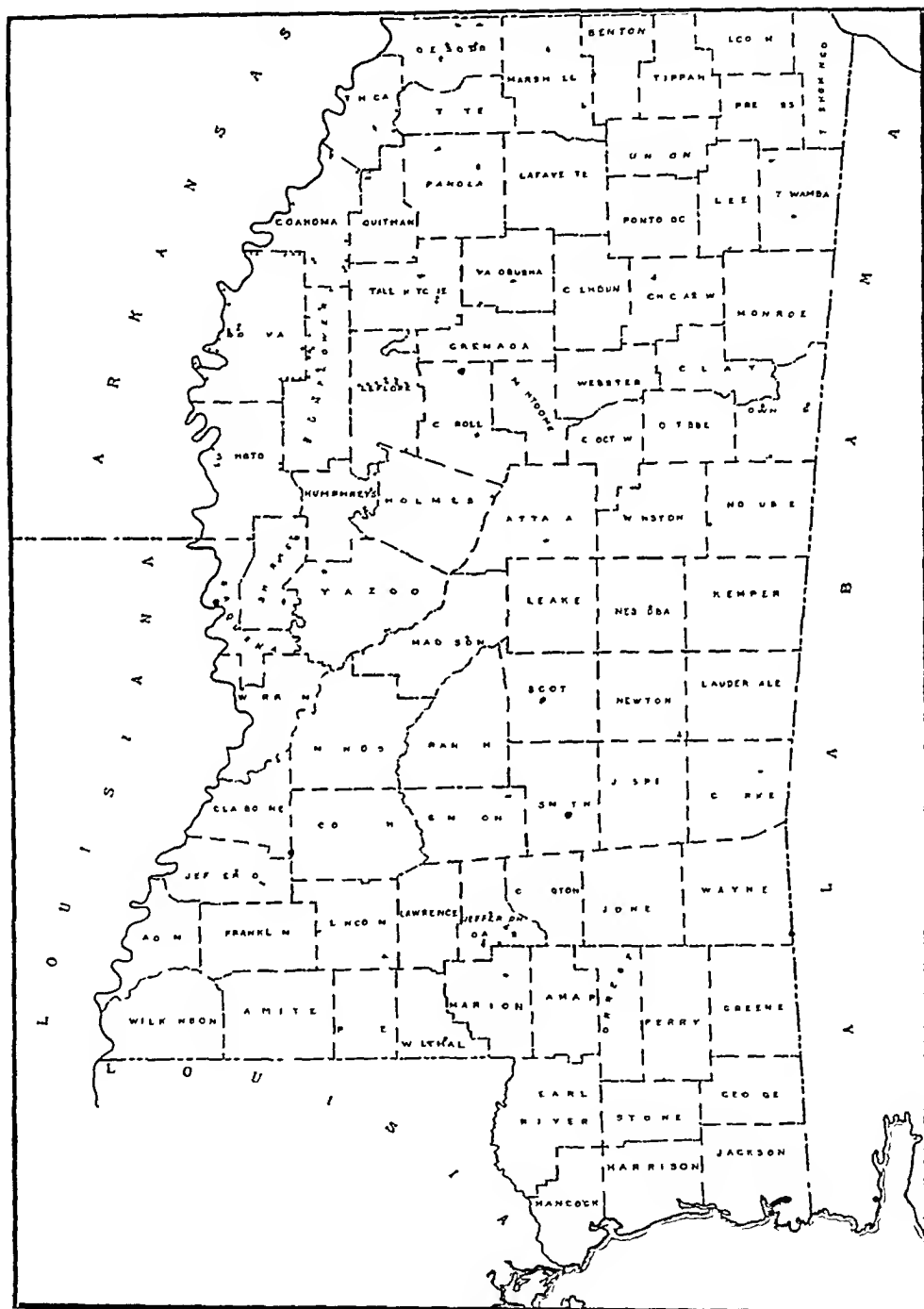


Chart 104—Mississippi, 1919 Distribution of cotton acreage (divided by 1,000)

In view of the data already presented tending to relate the distribution of pellagra to that of the planting of cotton, an index has been sought in the economics of the cultivation of cotton that might show

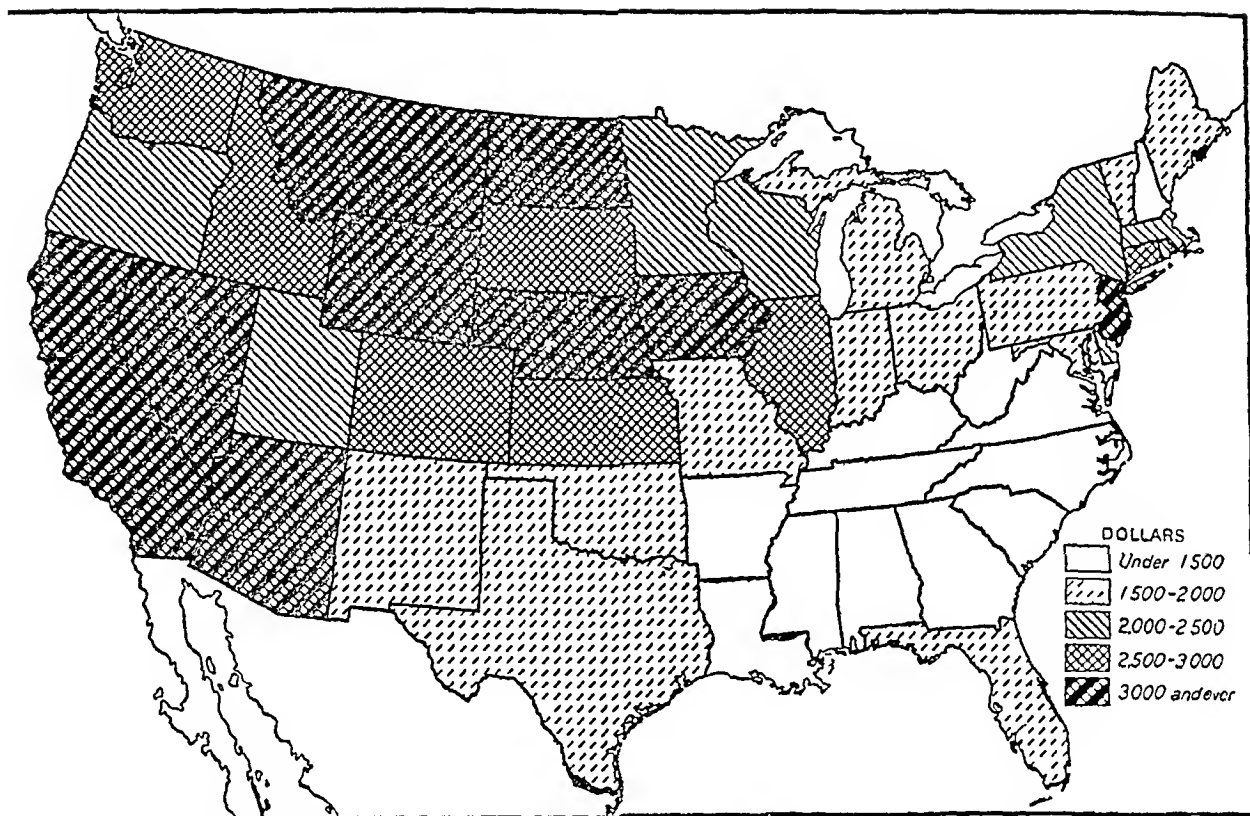


Chart 105—Annual gross income per farm, 1924-1928 (From the United States Department of Agriculture, Yearbook of Agriculture, 1930)

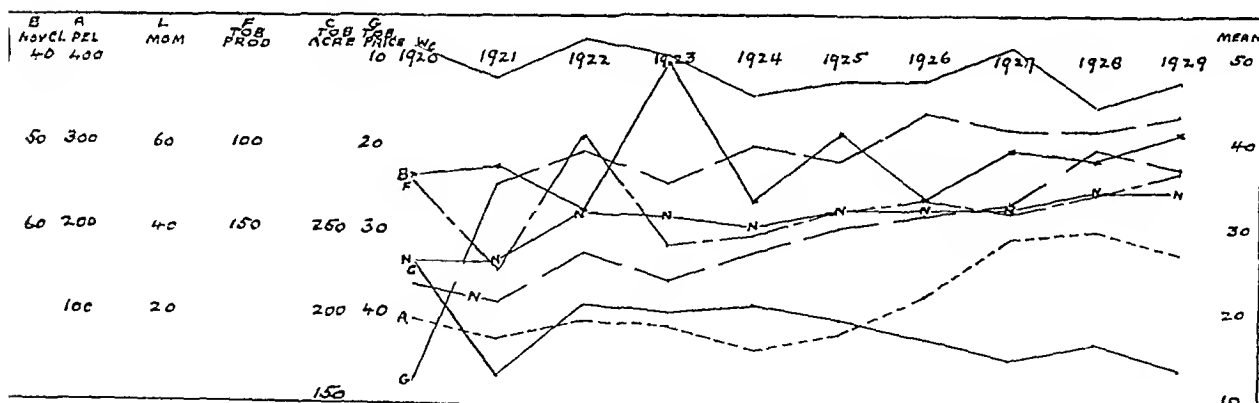


Chart 105—Virginia, from 1920 to 1929, inclusive Curve A indicates the incidence of pellagra in the first half year, from January to June, inclusive, curve WC, the winter cloudiness (December, January and February), an average of all stations, curve B, the cloudiness (sunshine) at Lynchburg the previous November Curve C the current year's tobacco acreage, curve F, the production of tobacco for the previous year (acreage multiplied by yield per acre), curve G, the previous December 1 price of tobacco, M, the previous November and December, current January and February incidence of pellagra, N, mean of November cloudiness (B), tobacco acreage (C), previous year's production of tobacco (F), previous December price of tobacco (G) and "momentum" from previous year (M)

some correspondence between the annual variation and annual variations in the incidence of pellagra, thus tending to illustrate and interpret the influence of economic conditions in the causation of pellagra, among the population planting cotton, as held by Goldberger and his associates—an attempt as applied to the rural population roughly parallel to the detailed study carried out by the Hygienic Laboratory (Hygienic

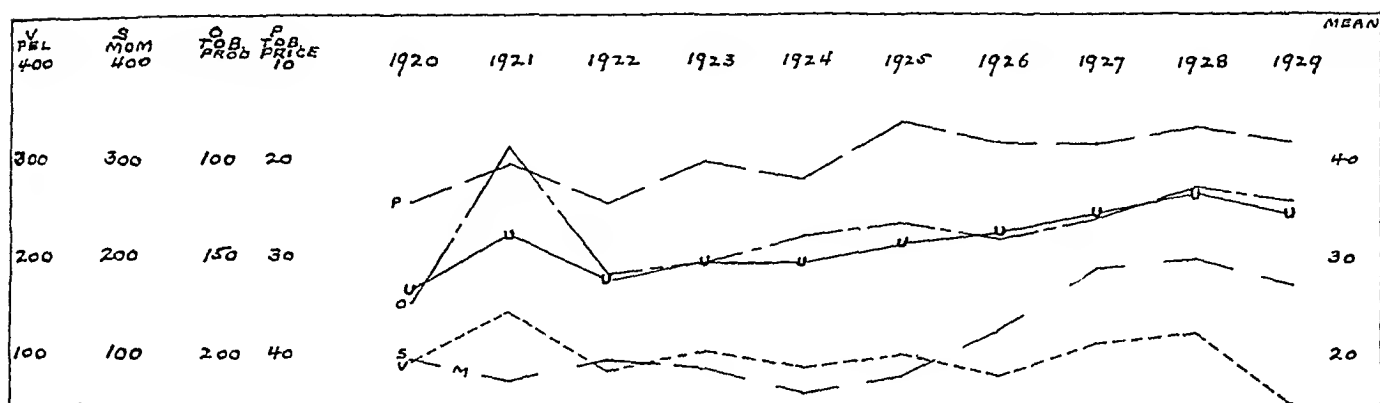


Chart 107—Virginia, from 1920 to 1929, inclusive. Curve *V* indicates the incidence of pellagra in the second half year, from July to December, inclusive, curve *O*, the production of tobacco for the current year, curve *P*, the price of tobacco for the current year, curve *S-M*, the incidence of pellagra in the first half of the current year, curve *U*, the mean of the current year's production of tobacco (*O*), the current year's price of tobacco (*P*) and the "momentum" from the first half of the current year (*S*)

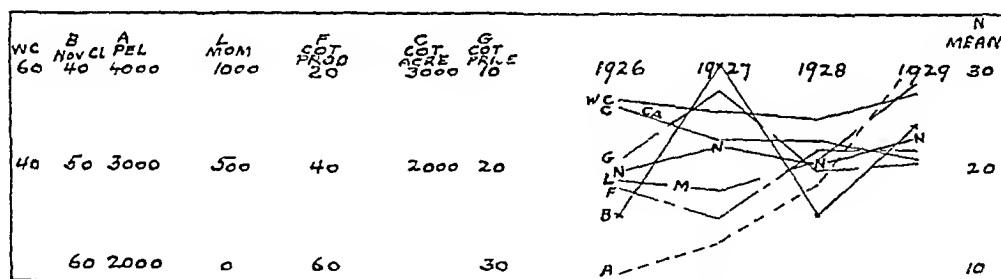


Chart 108—South Carolina, from 1926 to 1929, inclusive. Curve *A* indicates the incidence of pellagra in the first half year, from January to June, inclusive, curve *WC*, the winter cloudiness (December, January and February), an average of all stations, curve *B*, the cloudiness (sunshine) at Greenville the previous November, curve *C-CA*, the current year's cotton acreage, curve *F*, the production of cotton for the previous year (acreage multiplied by yield per acre), curve *G*, the previous December 1 price of cotton, curve *L-M*, the previous November and December, current January and February incidence of pellagra, curve *N*, the mean of the November cloudiness (*B*), the cotton acreage (*C*), previous year's production of cotton (*F*), previous December price of cotton (*G*) and the "momentum" from the previous year (*L*)

Laboratory Bulletin,⁴⁵ p 117) in cotton-mill villages in South Carolina. For this purpose the following facts seem pertinent

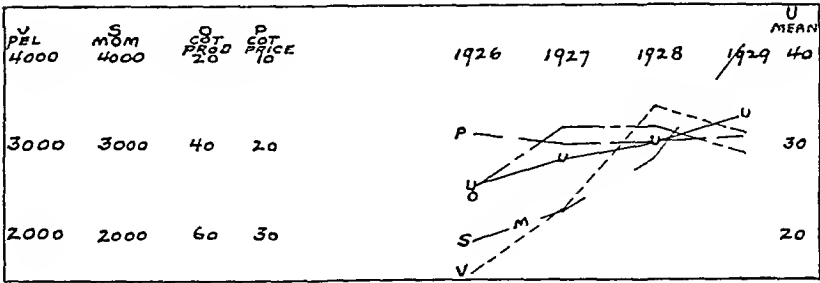


Chart 109—South Carolina, from 1926 to 1929, inclusive Curve *V* indicates the incidence of pellagra in the second half year, from July to December, inclusive, curve *O*, the production of cotton for the current year, curve *P*, the price of cotton for the current year, curve *S-M*, the incidence of pellagra in the first half of the current year, curve *U*, the mean of the current year's production of cotton (*O*), the current year's price of cotton (*P*) and the "momentum" from the first half of the current year (*S*)

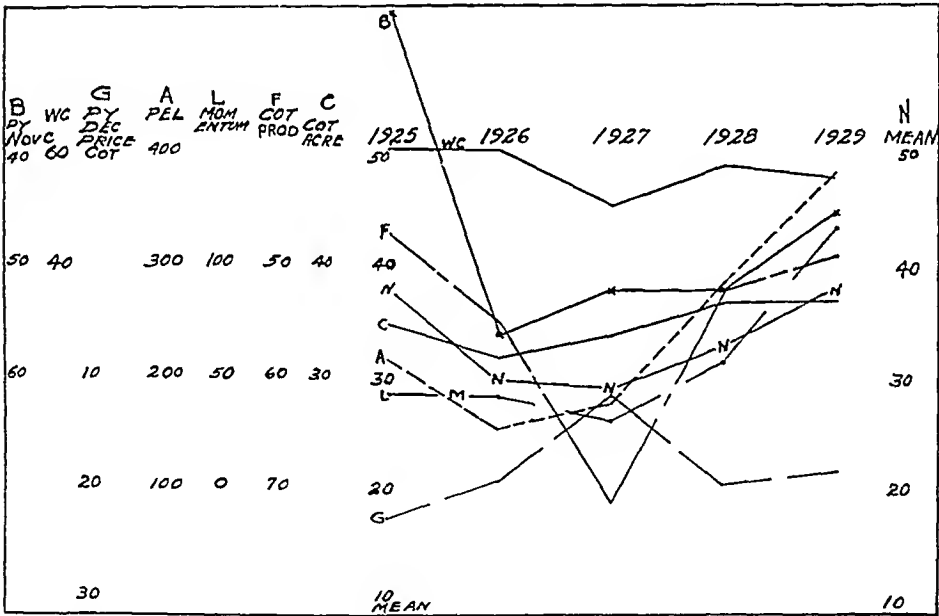


Chart 110—Georgia, from 1925 to 1929, inclusive Curve *A* indicates the incidence of pellagra in the first half year, from January to June, inclusive, curve *W/C*, the winter cloudiness (December, January and February), an average of all stations, curve *B*, the cloudiness (sunshine) at Atlanta the previous November, curve *C*, the current year's cotton acreage, curve *F*, the production of cotton for the previous year (acreage multiplied by yield per acre), curve *G*, the previous December 1 price of cotton, curve *L-M*, the previous November and December, current January and February incidence of pellagra, curve *N*, the mean of November cloudiness (*B*), cotton acreage (*C*), the previous year's production of cotton (*F*), the previous December price of cotton (*G*) and the "momentum" from the previous year (*L*)

In general, the annual gross income per farm ¹⁰⁸ is lowest in an area corresponding to the distribution of cotton and pellagra, though it is not strictly so limited (chart 105)

The cotton is planted in the late spring and early summer, and is marketed by farmers,¹⁰⁸ as is illustrated for 1928

	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar	April	May	June	July
Per cent	46	156	248	208	128	54	40	48	18	16	19	19

This tabulation shows that 78.6 per cent of the crop is marketed from August to December, inclusive

Of the farms in the cotton belt, from 50 to 66 per cent are operated by tenants ¹⁰³. These farmers and many who own their farms raise and market the crop largely through the medium of credit, with little money in hand or reserve of cash at any time of the year. These conditions suggest that during the first half of the year the economic status of the farmer who markets a single crop (cotton) depends largely on the production and price of cotton for the previous six months, and that his economic status for the second half of the year depends largely on the production and price of cotton for the current period.¹⁰⁴ For this reason, the production of cotton (acreage multiplied by yield per acre) for the previous year (*F* in the charts) and the price on the previous December 1 (*G* in the charts) have been selected as economic indexes for the first half of a current year. The curves for these factors, production and price, have been plotted separately, rather than multiplied in order to obtain a total value of the crop. Aside from a *possible* reasons that might favor plotting the curves for production and price separately, there is apparently a closer correlation between these curves so plotted and the curve of the incidence of pellagra than between a curve of the value of the entire crop of cotton and the incidence of pellagra. The scale of all economic factors is reversed so as to represent a decreased value by a rise in the curve to correspond with the suspected influence of economic depression tending to a rise in the incidence of pellagra.

¹⁰⁴ There seems to be no reasonable doubt that there is a direct correlation between the planting of cotton and the incidence of pellagra, but interpretation of the statistics introduces several possibilities. Reference has been made to exposure to sunlight as a possible positive (climatic) influence and to acreage as a factor in the value of the crop as a possible negative (economic) influence. Neither of these points of view takes into account still another consideration, viz., the extent to which the planting of cotton crowds out the planting of gardens, ownership of livestock and poultry and other agricultural pursuits tending to supply the population with pellagra-preventive foodstuffs. This phase of the economics of the planting of cotton in relation to the etiology of pellagra has been emphasized by Wheeler and others. At least it would appear that the relation of the planting of cotton to the incidence of pellagra might be advantageously subjected to further investigation.

In the second half of the year the curve for the production of cotton (*O*) is the same as that in the first half (*F*), but is plotted currently for the year, and the curve for the price of cotton (*P*) represents the current price for August 1 rather than for that of the previous December (*G*)

In chart 126, the curves for deaths from pellagra (*Z*) and the incidence of pellagra (*AV*) represent these data for the whole year rather than for the first or second half and the curve *Y* represents the farm value of the cotton for the previous December 1 (acreage multiplied by yield per acre times price)

In representing climatic factors possibly related to the incidence of pellagra, the curve of winter cloudiness (*WC*) is plotted in connection with the data for the first half of the year for each state. Graphically,

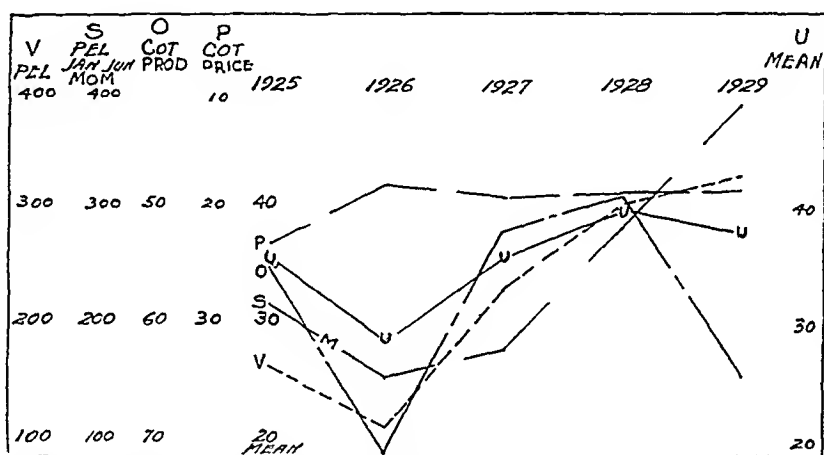


Chart 111—Georgia, from 1925 to 1929, inclusive. Curve *V* indicates the incidence of pellagra in the second half year, from July to December, inclusive, curve *O*, the production of cotton for the current year, curve *P*, the price of cotton for the current year, curve *S-M*, the incidence of pellagra in the first half of the current year, curve *U*, the mean of the current year's production of cotton (*O*), the current year's price of cotton (*P*) and the "momentum" from the first half of the current year (*S*)

with the exception of Virginia, a general and direct correlation is not suggested, and the curve has not been included in the means derived from the other plotted curves. There is here an apparent and possibly a real contradiction to the suggested influence of cloudiness in winter in contrast to solar exposure in summer as involving a significant principle of change from accustomed conditions. As previously stated and as illustrated by chart 24, the supposed principle of the influence of unaccustomed exposure to solar rays may have a greater validity than is indicated by the measure adopted, i. e., average cloudiness at all stations within a given state for

December, January and February, the exposure to solar rays during the spring and summer being regarded as constant. As an illustration of the possibility of a nearer approach to conditions of reality by observing a different index of shifting exposure to solar rays (charts 106, 108, 110, 112, 114, 116, 118, 120 and 122) cloudiness in the previous November at the Weather Bureau station nearest the center of the cotton belt for the state is plotted on a reversed scale, so that an upward peak indicates an excess of sunshine in November. If, in relation to this factor, winter cloudiness is regarded as constantly high

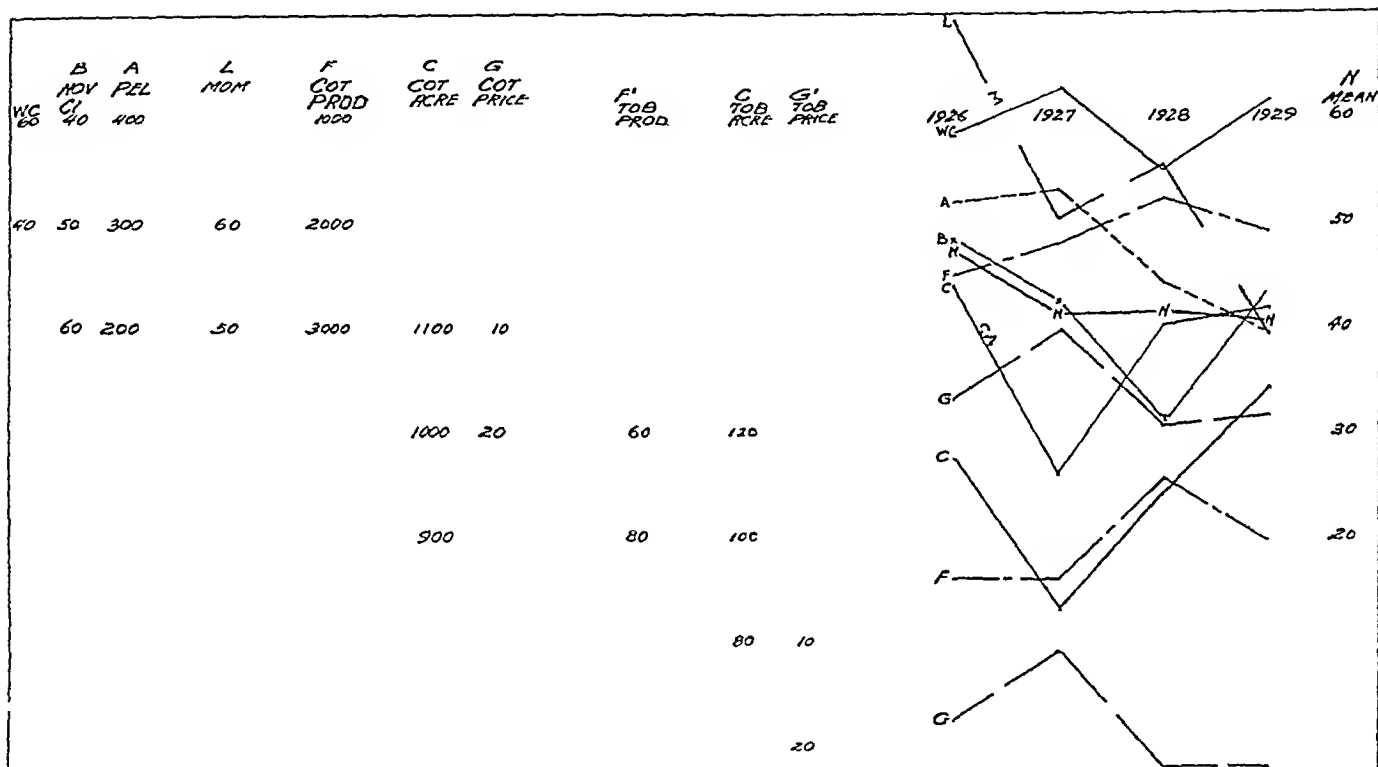


Chart 112—Tennessee, from 1926 to 1929, inclusive Curve *A* indicates the incidence of pellagra in the first half year, from January to June, inclusive curve *W/C*, the winter cloudiness (December, January and February), an average of all stations, curve *B₁*, the cloudiness (sunshine) at Memphis the previous November, curve *C-CA*, the current year's cotton acreage, curve *C'*, the current year's tobacco acreage, and *F*, the production of cotton for the previous year (acreage multiplied by yield per acre), curve *F'*, the production of tobacco for the previous year, curve *G* the previous December 1 price of cotton, curve *G'*, the previous December 1 price of tobacco, curve *L-M*, the previous November and December, current January and February incidence of pellagra, curve *N*, the mean of November cloudiness (*B*) cotton acreage (*C*), the previous year's production of cotton (*F*), the previous December price of cotton (*G*) and the "momentum" from the previous year (*L*)

1 e , sunshine constantly low, there would be a change in exposure to solar rays from an excess of sunshine in November when it occurs,

to low sunshine in winter (exaggerated in certain years, as 1927) and back again to the relatively high percentage of possible sunshine (reduced cloudiness) and relatively unfiltered solar rays (reducing air mass traversed) in spring and summer. The inclusion of this curve of previous November cloud (*B*) appears to favor a closer correlation of all the factors under consideration with annual variations in the incidence of pellagra than is obtained without the factor *B*.

Since the data presented (charts 28 to 69) indicate a close correlation between the incidence of pellagra and an increased exposure to solar rays, it would seem probable that the annual acreage of cotton planted would in some degree determine the exposure of the population planting cotton to solar rays near the summer solstice, and in this

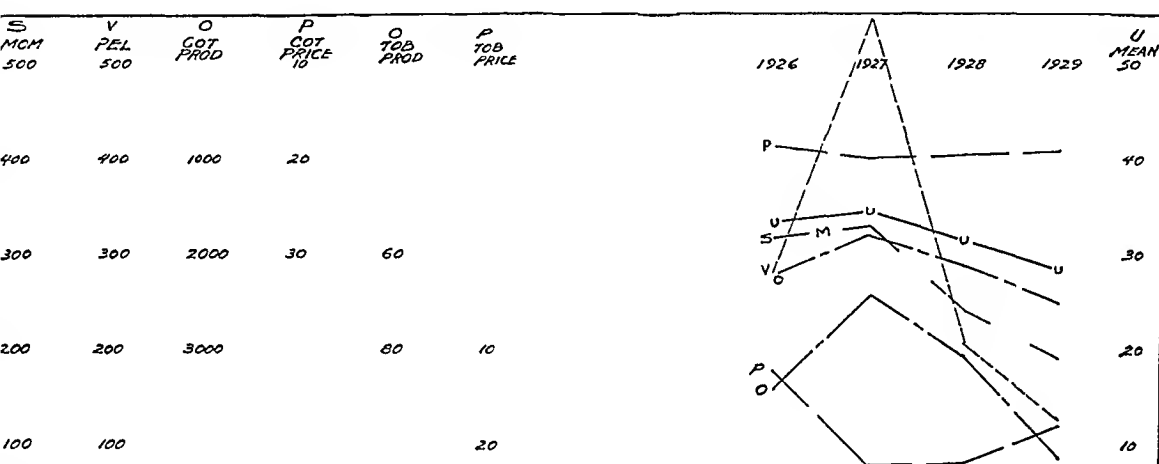


Chart 113—Tennessee, from 1926 to 1929, inclusive. Curve *V* indicates the incidence of pellagra in the second half year, from July to December, inclusive, curve *O* the production of cotton for the current year, curve *O'*, the production of tobacco for the current year, curve *P*, the price of cotton for the current year, curve *P'*, price of tobacco for the current year, curve *S-M*, the incidence of pellagra in the first half of the current year, curve *U*, the mean of the current year's production of cotton (*O*), the current year's price of cotton (*P*) and the 'momentum' from the first half of the current year (*S*).

sense would be regarded as a climatic factor as distinguished from an economic factor. The curve for this factor is plotted in charts 106, 108, 110, 112, 114, 116, 118, 120 and 122 as *C*, and since the supposed relation to the incidence of pellagra is direct, the scale is not reversed as it is for curves *F* and *O*, in which cotton acreage is regarded as a factor in the economics of the cultivation of cotton.

The possibility that conditions tending to the production of pellagra in one year may have an influence on the incidence of pellagra the following year has been referred to under the designation "delayed inci-

dence" or "momentum" When it is considered that the seasonal incidence of pellagra tends to reach a low level in November and to remain low till spring, it would appear that the incidence of the disease during November, December, January and February may in some degree constitute an index of this factor of "momentum," and in charts 106, 108, 110, 112, 114, 116, 118, 120 and 122 the curve *L* represents the reported incidence of pellagra for the four months named

In charts 107, 109, 111, 113, 115, 117, 119, 121 and 123 for the second half of the year, the incidence of pellagra during the first half of the current year has been plotted (*S*) as a similar factor of

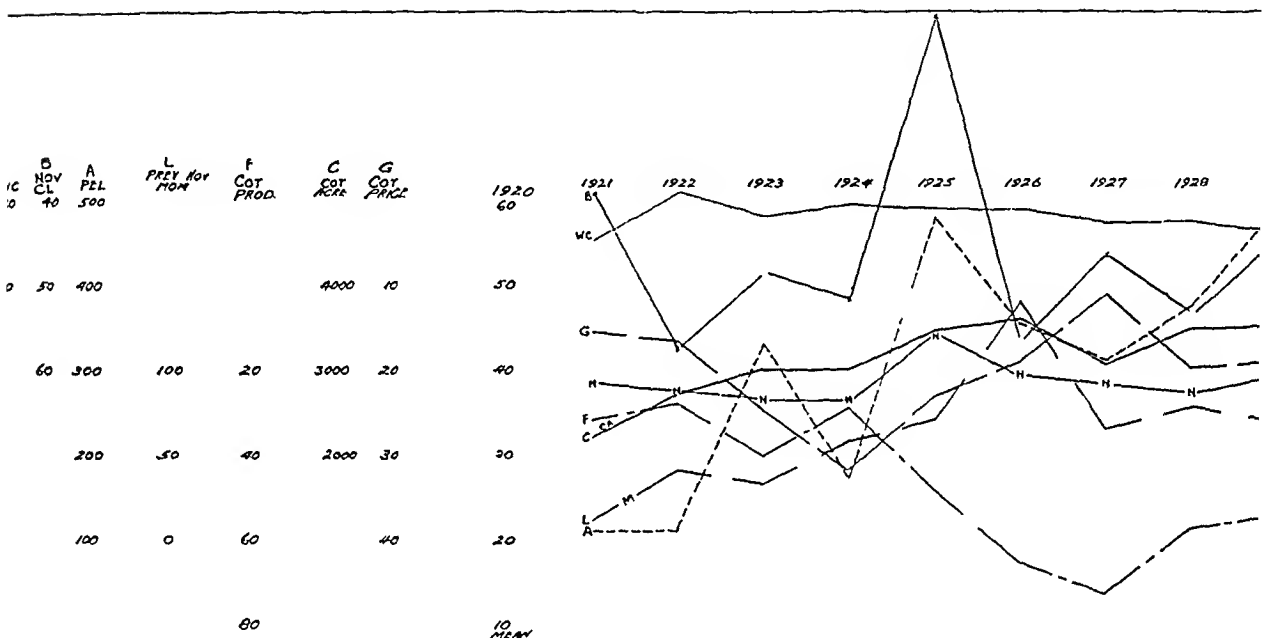


Chart 114—Alabama, from 1921 to 1929, inclusive. Curve *A* indicates the incidence of pellagra in the first half year, from January to June, inclusive, curve *W.C.*, the winter cloudiness (December, January and February), an average of all stations, curve *B*, the cloudiness (sunshine) at Montgomery the previous November, curve *C-CA*, current year's cotton acreage, curve *F*, the production of cotton for the previous year (acreage multiplied by yield per acre), curve *G*, the previous December 1 price of cotton, curve *L-M*, the previous November and December, current January and February incidence of pellagra, curve *N*, the mean of November cloudiness (*B*), cotton acreage (*C*), previous year's production of cotton (*F*), previous December price of cotton (*G*) and the "momentum" from the previous year (*L*)

"momentum," a lag or a delayed effect of influences operative during the first half of the year

* For 1920, the incidence of pellagra for the months of January and February multiplied by 2 is used in lieu of November and December, 1919, and January and February, 1920

Of the figures for the first half of the year, the curve *N* represents the mean of the two "climatic" factors *B* and *C*, the two "economic" factors *F* and *G* and the factor of "momentum" *L*.

Of the figures for the second half of the year, the curve *U* represents the mean of the two "economic" factors *O* and *P* and the factor of "momentum" *S*.

Charts 124 and 125 represent the first and second half years, respectively, for the four states for which data of the incidence of pellagra are available from 1920 to 1929, inclusive. Curve *E* (chart 124) is the mean of "climatic" factors *B* and *C*. Curve *I* is the mean of "economic" factors *F* and *G*. Curve *N* is the same curve as that described, the mean of the five factors represented by *B*, *C*, *F*, *G* and *L*. Curve *R* (chart 125) is the mean of "economic" factors *O* and *P*. Curve *U* is the same as that described, the mean of the three factors *O*, *P* and *S*.

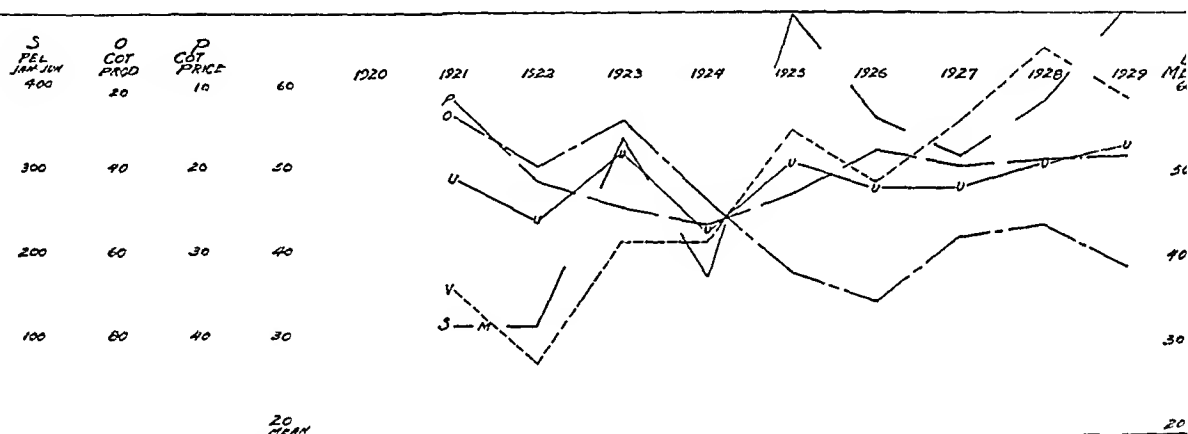


Chart 115—Alabama from 1921 to 1929, inclusive. Curve *V* indicates the incidence of pellagra in the second half year, from July to December, inclusive, curve *O*, the production of cotton for the current year, curve *P*, the price of cotton for the current year, curve *S-M*, the incidence of pellagra in the first half of the current year, curve *U*, the mean of the current year's production of cotton (*O*), the current year's price of cotton (*P*) and the "momentum" from the first half of the current year (*S*).

If Mississippi (charts 116 and 117), the state with the highest reported incidence of pellagra, is selected for examination, the following observations with reference to correlations with the curve of the incidence of pellagra appear to be justified, and, it is believed that they are in the main supported by the figures for other states. In chart 116, the curve of previous November cloudiness (*B*) is close from 1920 to 1927. The curve of cotton acreage (*C*) shows little annual conformity, but a conformity in a general upward trend. The curve of the production of cotton (*F*) is quite close in the period from 1925 to 1928. The curve of the price of cotton (*G*) is in rough general conformity. The

curve of "momentum" (L) is in general conformity. The curve N of the mean of the five factors mentioned appears to indicate that in the two "economic" factors, the two "climatic" factors and the factor of "momentum" the major factors bearing on the annual incidence of pellagra in a given state are comprehended. Similar observations with reference to chart 117 appear to be warranted, but a closer correlation of the curve of the price of cotton (P) from 1920 to 1925 is noted.

The exceptional peak in the incidence of pellagra (V) in the second half of the year in Arkansas in 1921 and 1927 (chart 119) is noteworthy. It would seem possible that in 1927 the delay in the planting

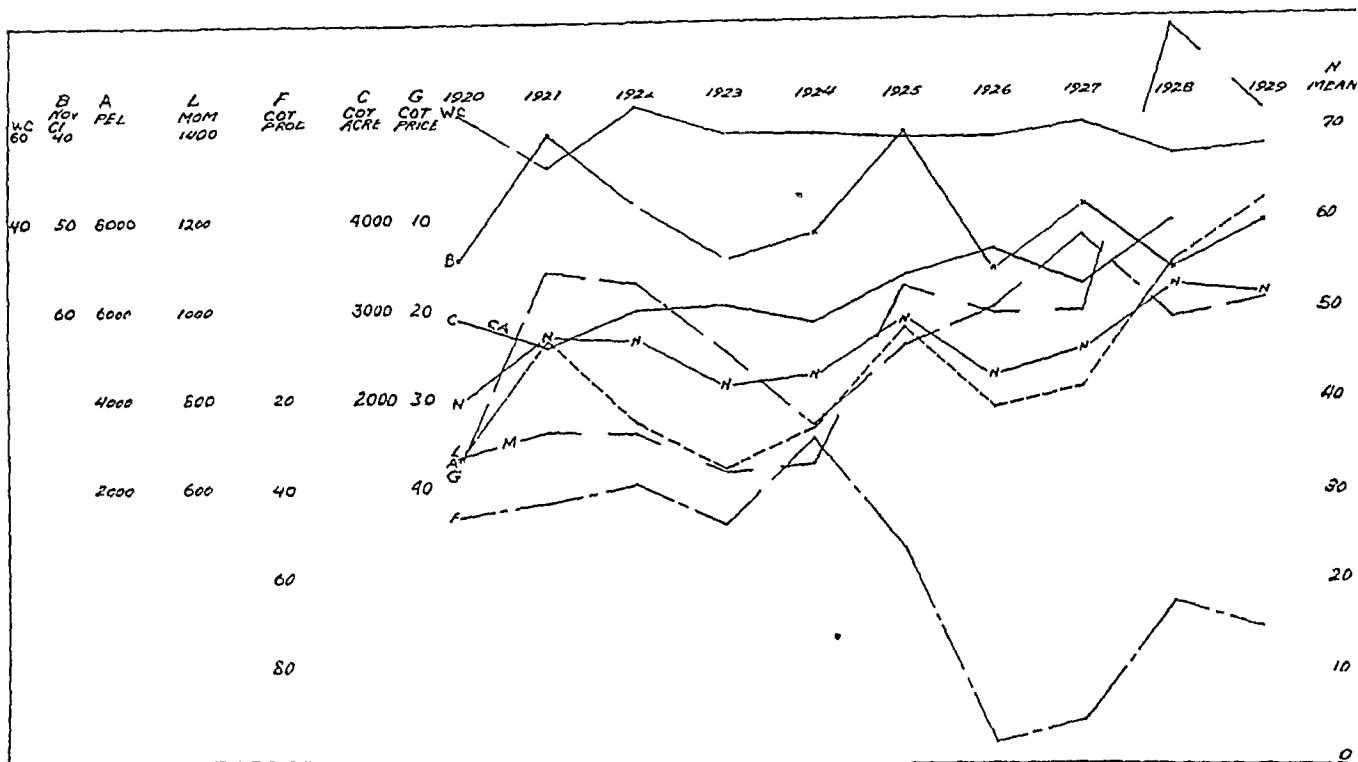


Chart 116—Mississippi, from 1920 to 1929, inclusive. Curve A indicates the incidence of pellagra in the first half year, from January to June, inclusive, curve $W.C.$, the winter cloudiness (December, January and February), an average of all stations. B , cloudiness (sunshine) at Vicksburg the previous November, curve $C-CA$, the current year's cotton acreage, curve F , the production of cotton for the previous year (acreage multiplied by yield per acre), curve G , the previous December 1 price of cotton, curve $L-M$, the previous November and December, current January and February incidence of pellagra, curve N , the mean of November cloudiness (B), cotton acreage (C), the previous year's production of cotton (F), the previous December price of cotton (G) and the "momentum" from the previous year (L).

of cotton, owing to the flood in the Mississippi Valley, might rationally require a transfer of curve C (chart 118) to chart 119 for 1927, and that this would also apply in some measure to other states included in the flood area, such as Tennessee, Mississippi and Louisiana. As for

the peak of the incidence of pellagra in the latter half of 1921 in Arkansas, in a personal communication, Dr C W Garrison, State Health Officer for Arkansas, stated

The number of pellagra cases reported for Arkansas for August, 1921, was 1,395. The reason for this high number at that time was that I sent out a request letter and urged all cases to be reported as that was a high pellagra year following the depression of 1920. Under normal conditions a great majority of the pellagrins do not call a physician until they are bedridden.

In chart 124, the curve *N*, representing the mean of five factors (*B*, *C*, *F*, *G* and *L*), appears to correlate somewhat more closely with that of the incidence of pellagra (*A*) than does either curve *E* (of the

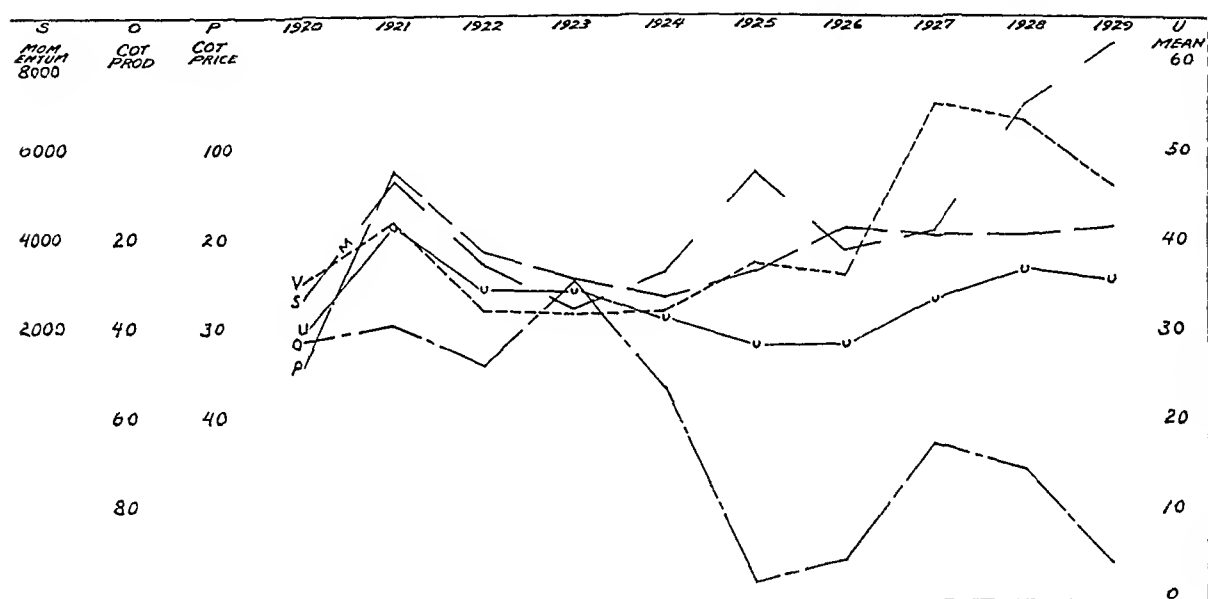


Chart 117—Mississippi, from 1920 to 1929, inclusive. Curve *V* indicates the incidence of pellagra in the second half year, from July to December, inclusive, curve *O*, the production of cotton for the current year, curve *P*, the price of cotton for the current year, curve *S-M*, the incidence of pellagra in the first half of the current year, curve *U*, the mean of the current year's production of cotton (*O*), the current year's price of cotton (*P*) and the 'momentum' from the first half of the current year (*S*)

two "climatic" factors *B* and *C*) or curve *I* (of the two "economic" factors *F* and *G*). In chart 125, there is but little apparent difference in the correlation between the curve of the incidence of pellagra (*V*), curve *R* (the mean of "economic" factors *O* and *P*) and curve *U* (the mean of *O* and *P* and the factor of "momentum" *S*)

In chart 126, the interest lies chiefly in the fact that it introduces a curve of the deaths from pellagra (*Z*) in the United States Registration Area from 1913 to 1928. There is a degree of annual conformity

between this curve (*Z*) and the curve of the value of cotton (*Y*) sufficient to regard it as tending to confirm the opinion of the Goldberger school relative to the significance of economic conditions in the epidemiology of pellagra, at least with respect to annual variations. There appears to be only a rough conformity of the incidence of pellagra as reported with the mortality from pellagra as reported, it is seen more in the general trend than in the annual variation. The insert showing the relation of rural to urban deaths from pellagra from 1925 to 1927, inclusive, gives a ratio of approximately 3 : 1.

Humidity—It is generally recognized that relative humidity and the temperature of the atmosphere, together with the movement of the air and intake of food, are interrelated in their effect on bodily com-

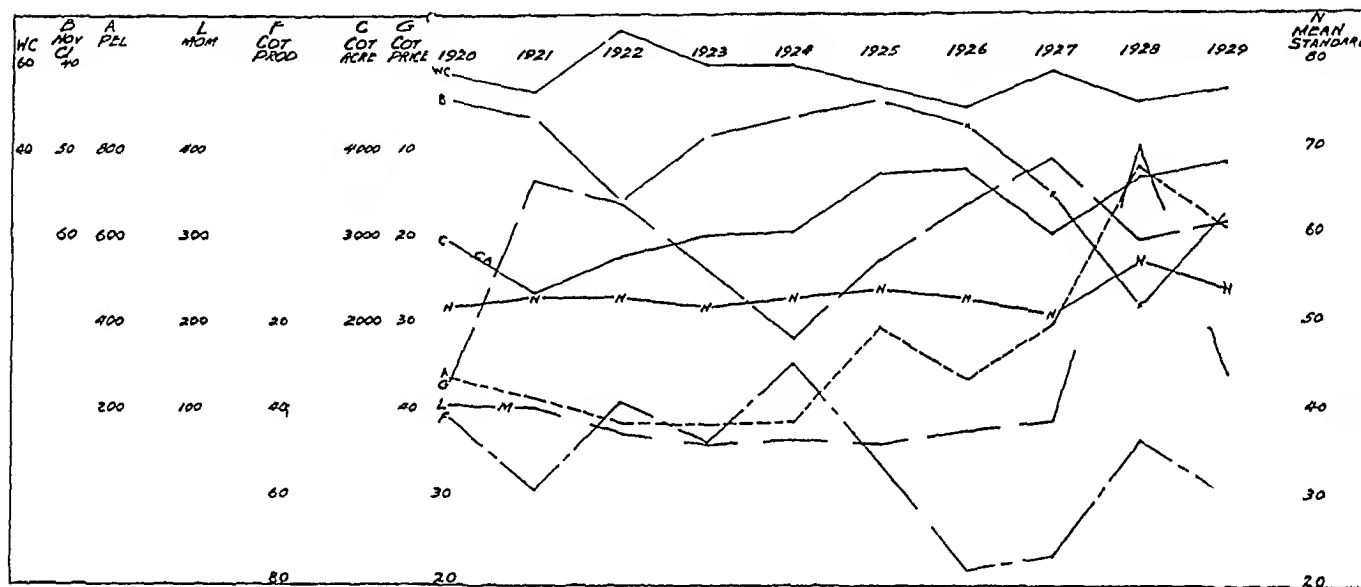


Chart 118—Arkansas, from 1920 to 1929, inclusive. Curve *A* indicates the incidence of pellagra in the first half year, from January to June, inclusive, curve *WC*, the winter cloudiness (December, January and February), an average of all stations, curve *B*, the cloudiness (sunshine) at Little Rock the previous November, curve *C-CA*, the current year's cotton acreage, curve *F*, the production of cotton for the previous year (acreage multiplied by yield per acre), curve *G*, the previous December 1 price of cotton, curve *L-M*, the previous November and December, current January and February incidence of pellagra, curve *N*, the mean of November cloudiness (*B*), cotton acreage (*C*), previous year's production of cotton (*F*), previous December price of cotton (*G*) and the "momentum" from the previous year (*L*).

fort, physical and mental efficiency and metabolism (Lusk⁶⁶ and McConnell, Yagloglou and Fulton⁷³)

The best combination of all is probably air at about 67° F and 80 per cent relative humidity, with a barely perceptible movement. A departure from these conditions in any direction diminishes people's comfort, reduces their capacity to work, presumably increases their susceptibility to disease, and unquestionably

raises their death rate. The most favorable condition is a variable temperature whose average is the optimum. Each month in the year the same conditions are manifest: many deaths when the temperature rises, few when it falls (Huntington⁴⁴).

The influence of heat and humidity may extend through a twenty-four hour cycle, while that of solar radiation is limited to daylight only.

Sundstroem (quoted by Laurens⁵⁷) found that the light from mazda lamps acts as a stimulant to the growth of mice exposed to it at ordinary

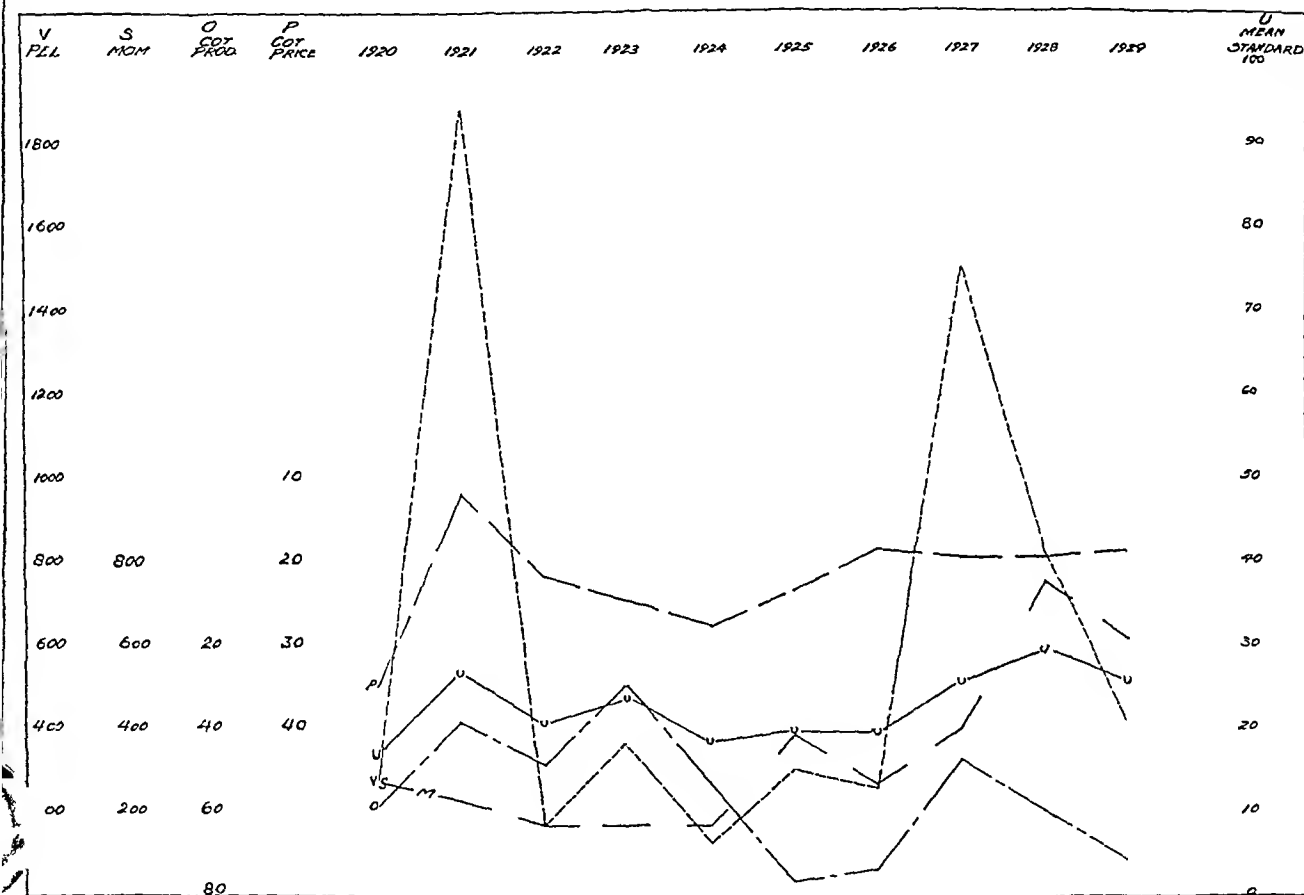


Chart 119—Arkansas, from 1920 to 1929, inclusive. Curve *V* indicates the incidence of pellagra in the second half year, from July to December, inclusive, curve *O*, the production of cotton for the current year, curve *P*, the price of cotton for the current year, curve *S-M*, the incidence of pellagra in the first half of the current year, curve *U*, the mean of the current year's production of cotton (*O*), the current year's price of cotton (*P*) and the "momentum" from the first half of the current year (*S*).

room temperature, but the retarding influence of stagnant humid air is added to by exposure to this artificial light. He found little evidence that tropical sunlight as such had any effect on the growth of rats, the harmful effect of a tropical climate seeming to be in the decrease in the cooling power of stagnant air.

Charts 127 and 128 show that in South Carolina in 1927 and 1928 the seasonal curve of relative humidity closely approximated that of cloudiness. The same charts and chart 129 (Virginia) show a tendency to a minimum relative humidity in the spring and a maximum humidity in August. Chart 130 shows this excess of humidity in August over

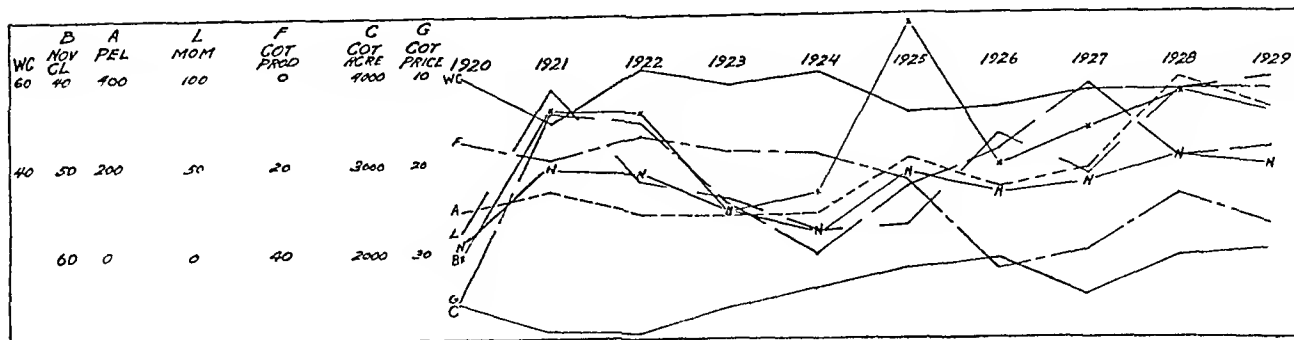


Chart 120—Louisiana, from 1920 to 1929, inclusive. Curve *A* indicates the incidence of pellagra in the first half year, from January to June, inclusive, curve *WC*, the winter cloudiness (December, January and February), an average of all stations, curve *B*, the cloudiness (sunshine) at New Orleans the previous November, curve *C*, the current year's cotton acreage, curve *F*, production of cotton for the previous year (acreage multiplied by yield per acre), curve *G*, the previous December 1 price of cotton, curve *L*, the previous November and December, current January and February incidence of pellagra, curve *N*, the mean of the November cloudiness (*B*), cotton acreage (*C*), the previous year's production of cotton (*F*), the previous December price of cotton (*G*) and the "momentum" from the previous year (*L*).

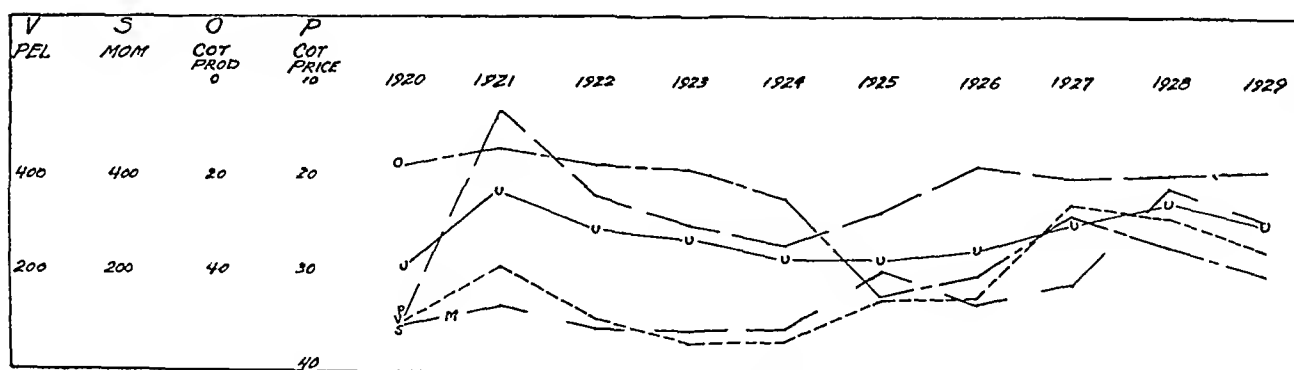


Chart 121—Louisiana, from 1920 to 1929, inclusive. Curve *V* indicates the incidence of pellagra in the second half year, from July to December, inclusive, curve *O*, the production of cotton for the current year, curve *P*, the price of cotton for the current year, curve *S-M*, the incidence of pellagra in the first half of the current year, curve *U*, the mean of the current year's production of cotton (*O*), the current year's price of cotton (*P*) and the "momentum" from the first half of the current year (*S*).

that in April as a phenomenon quite general to the pellagra belt and somewhat more accentuated in the areas with a heavier incidence of

pellagra and more planting of cotton (compare with chart 23) Chart 130 also shows the mean temperature for July in the same area. The relatively high humidity in August does not appear to depress the average metabolism during that month in Virginia (charts 21 and 22), though the rising humidity from spring through the summer may have such a tendency. It is noted also that the incidence of pellagra begins to decline before the maximum humidity is reached.

There is no apparent relation of the data shown in chart 130 to the geographic distribution and prevalence of pellagra further than that, in general, in the pellagra belt the temperature and humidity approximate the levels described by various authors as favorable to a minimum metabolism and to a low intake of protein.

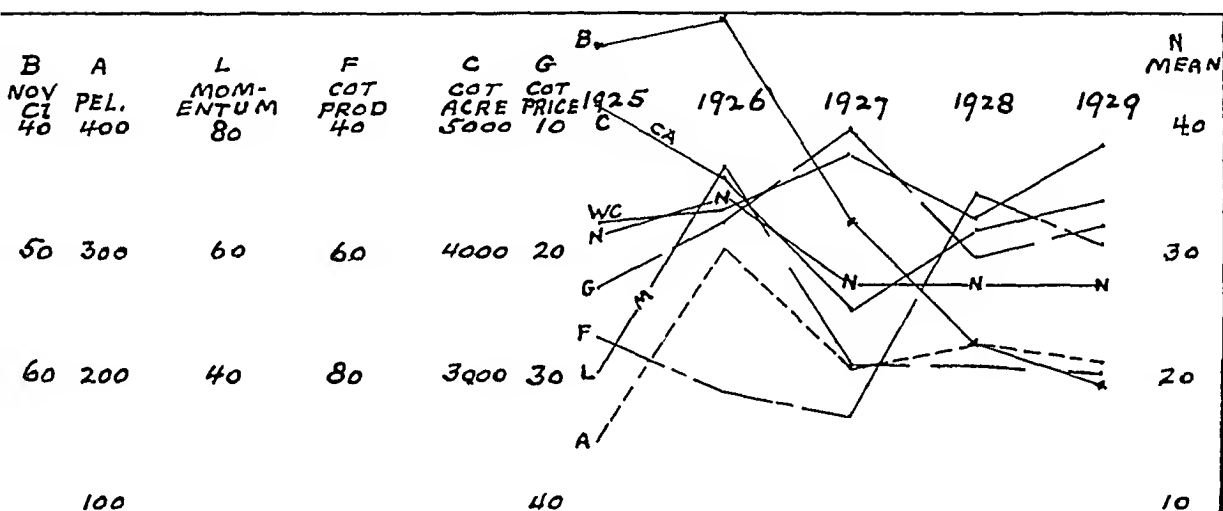


Chart 122—Oklahoma, from 1925 to 1929, inclusive. Curve *A* indicates the incidence of pellagra in the first half year, from January to June, inclusive, curve *WC*, the winter cloudiness (December, January and February) at Oklahoma City, curve *B*, the cloudiness (sunshine) at Oklahoma City the previous November, curve *C-CA*, the current year's cotton acreage, curve *F*, the production of cotton for the previous year (acreage multiplied by yield per acre), curve *G*, the previous December 1 price of cotton, *L-M*, the previous November and December, current January and February incidence of pellagra, curve *N*, the mean of November cloudiness (*B*), cotton acreage (*C*), the previous year's production of cotton (*F*), the previous December price of cotton (*G*) and the "momentum" from the previous year (*L*).

AREAS WITH A RELATIVELY HIGH PREVALENCE OF PELLAGRA

Consideration has been given the seasonal and annual incidence of pellagra. It is now proposed to examine factors possibly contributing to a relatively high prevalence from year to year and from season to season in a given area. The two states with the highest reported incidence are Mississippi and South Carolina, in the order named.

Under the title of "Bulletin W," the Weather Bureau of the United States Department of Agriculture issued a summary of the climatological data of the United States by sections, from the establishment of the stations to 1920, inclusive. Section 79, for northern Mississippi, comprises that portion of the state northward of the thirty-third par-

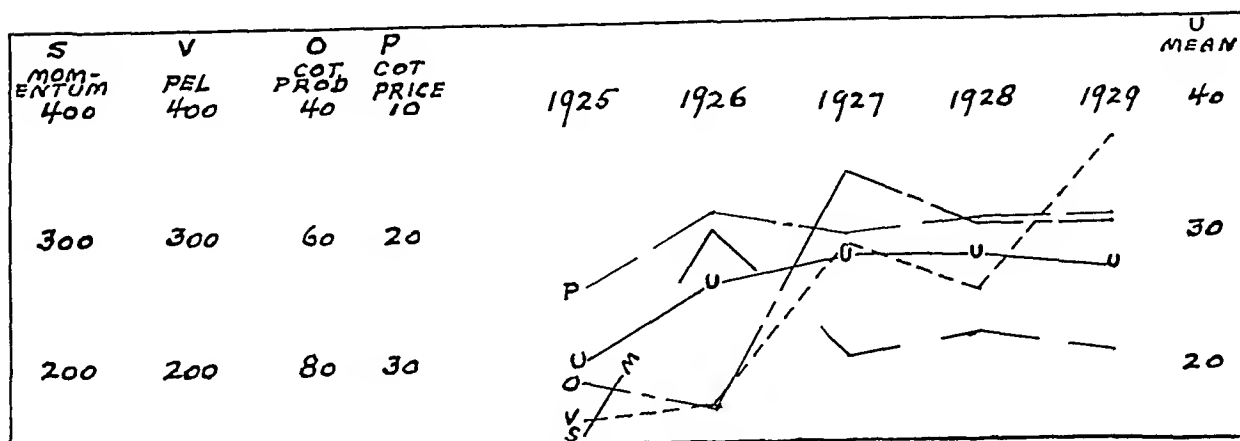


Chart 123—Oklahoma, from 1925 to 1929, inclusive. Curve *V* indicates the incidence of pellagra in the second half year, from July to December, inclusive, curve *O*, the production of cotton for the current year, curve *P*, the price of cotton for the current year, curve *S-M*, the incidence of pellagra in the first half of the current year, curve *U*, the mean of the current year's production of cotton (*O*), the current year's price of cotton (*P*) and the "momentum" from the first half of the current year (*S*)

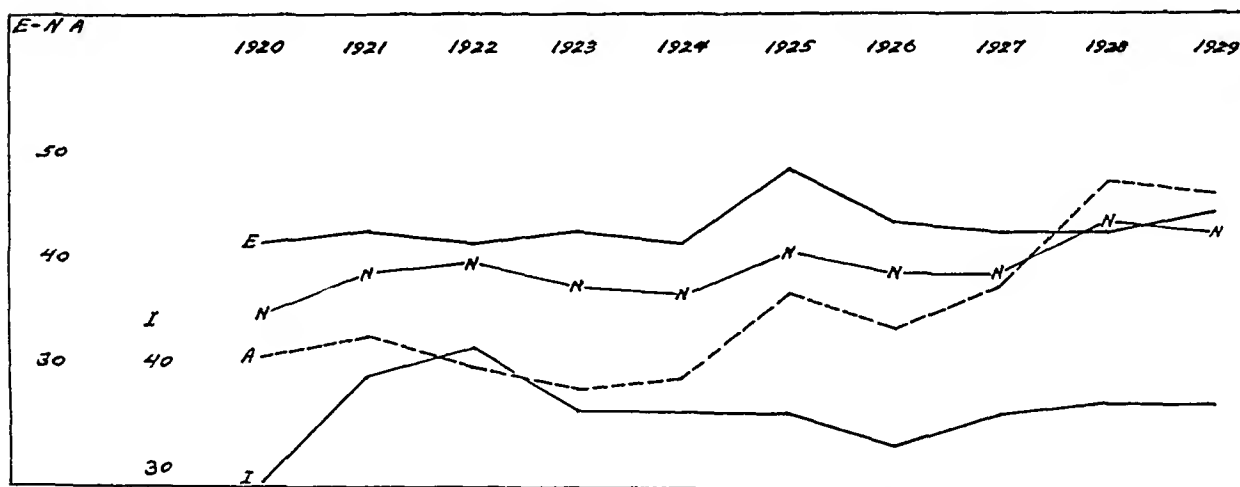


Chart 124—Composite data for four states, Virginia, Mississippi, Louisiana and Arkansas, for the first half of the year, from January to June, inclusive, and from 1920 to 1929, inclusive. Curve *A* indicates the incidence of pellagra, curve *E*, the mean of the previous November cloudiness (sunshine) and the current year's cotton acreage, curve *I*, the mean of the production of cotton (Virginia, tobacco) for the previous year and the previous December price of cotton (Virginia, tobacco), curve *N*, the mean of November cloudiness, cotton acreage, the previous year's production of cotton, the previous December price of cotton and the "momentum" from the previous year

allel, and section 80, for southern Mississippi, that portion of the state southward of that latitude. The general description of the northern section is as follows:

21,500 square miles, with no large urban population, the main industries being agriculture, lumbering or allied enterprises. The western portion of this division, the so-called Delta region, is mainly included between the Tallahatchie and Yazoo Rivers, on the east, and the Mississippi River on the west, an extremely fertile, level body of land, with alluvial soil, about 5,800 square miles in area. The mean annual temperature of the district is 62.6° , January average temperature is the lowest, 43.9° , and July the warmest, 80.4° . The heat is somewhat alleviated at intervals during the season from the middle of May to the end of September by the occurrence of thunder showers, with subsequent drop in tem-

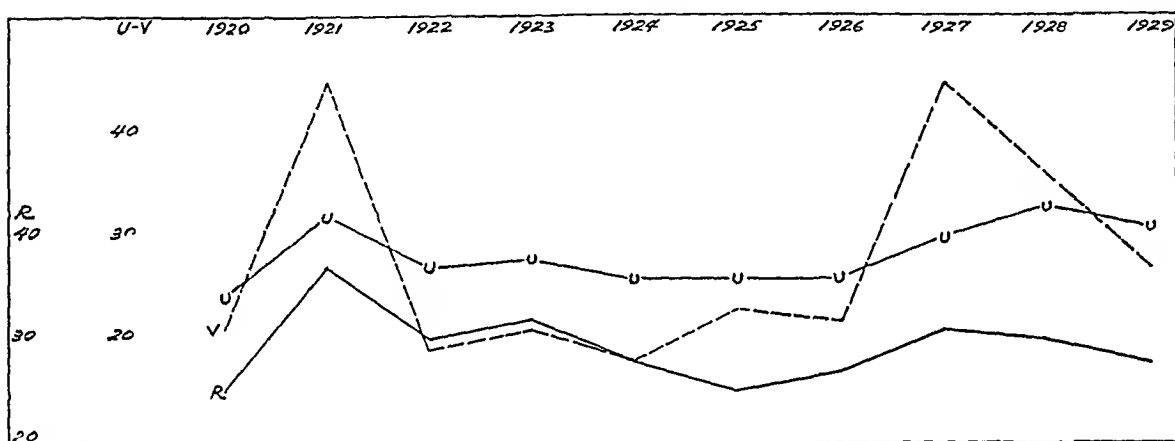


Chart 125—Composite data for four states, Virginia, Mississippi, Louisiana and Arkansas, for the second half of the year, from July to December, inclusive, from 1920 to 1929, inclusive. Curve *V* indicates the incidence of pellagra, curve *R*, the mean of production of cotton for the current year (Virginia, tobacco), and the price of cotton for the current year (Virginia, tobacco); curve *U*, the mean of the current year's production of cotton, the current year's price of cotton and the "momentum" from the first half of the year.

perature of short duration, otherwise this heated period is very oppressive, the air continuing moist. Maximum temperatures of 100° , or higher, occur with greatest frequency during July and August, but occasionally are recorded during other months of this season.

The general description of the southern section is as follows:

There are no large cities and the main occupation is agriculture, or some allied industry. The summers are long and hot, the winters short and mild. Temperatures of 100° , or over, occasionally occur in the interior in midsummer and as night temperatures are high at that time of the year, and the humidity also, with little air movement, the summer climate is somewhat oppressive. Air circulation, due to land and sea breezes, serves to alleviate the hot and humid atmospheric condition throughout the region adjacent to the coast.

It will be manifest that such a climate, whatever relations of cause and effect are or are not involved, is not unfavorable to the production of cotton and to the development of pellagra

Examination of charts 25, 85, 91 and 103 shows the coastal areas of Virginia, North Carolina, South Carolina and Mississippi to be relatively free from pellagra. With variations in altitude, the climatic factors vary considerably as regards light, humidity (chart 130), temperature and the movement of air. The agricultural pursuits are different (charts 82, 86, 87, 92 and 104). The population hardly appears

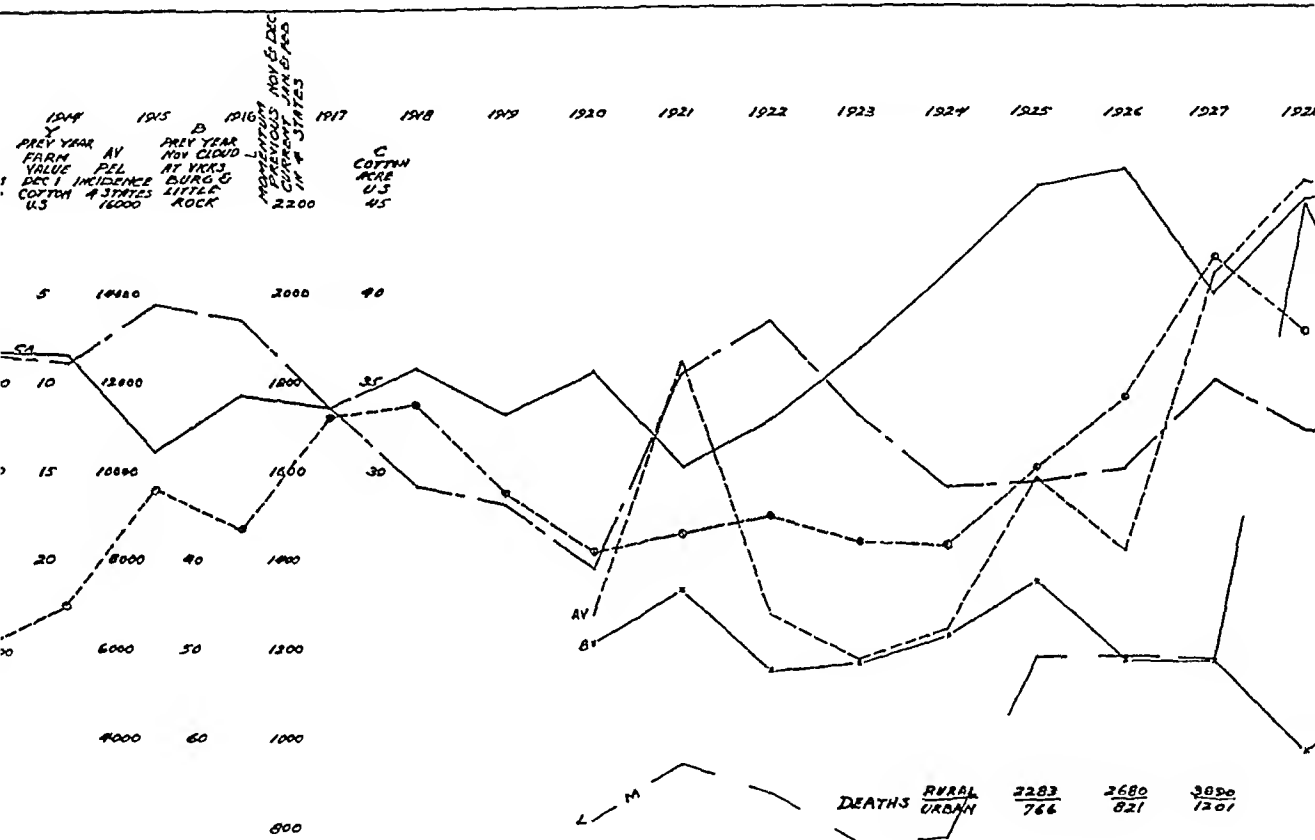


Chart 126—Deaths from pellagra, incidence of pellagra, certain economic values and certain climatic values. Curve Z, indicates the deaths from pellagra in the United States Registration Area, from 1913 to 1928, inclusive, curve AV, the incidence of pellagra in four states, Virginia, Mississippi, Louisiana and Arkansas, from 1920 to 1929, inclusive, curve B1, average of the previous November cloudiness (sunshine) at Vicksburg and Little Rock, curve C-CA, the current year's cotton acreage in the United States, curve Y, the previous December 1 farm value of cotton for the United States, curve L-M, the previous November and December, current January and February incidence of pellagra in four states, Virginia, Mississippi, Louisiana and Arkansas

to be a consistent variable. The various combinations in this multiplicity of factors are numerically great and give rise to many unanswered questions. Do climatic conditions directly influence the incidence

of pellagra or may they tend primarily to influence the content of the "pellagra-preventive" factor in the vegetable and animal food of the district? Do certain climatic conditions tend to favor the production of cotton, tobacco and other crops planted in a "high sun" and thus cause excessive exposure, or do they crowd out other crops that would tend toward the prevention of pellagra? * Many of the same complex interpretations are involved in the question as to why pellagra is not more generally prevalent in the areas referred to by Huntington "In

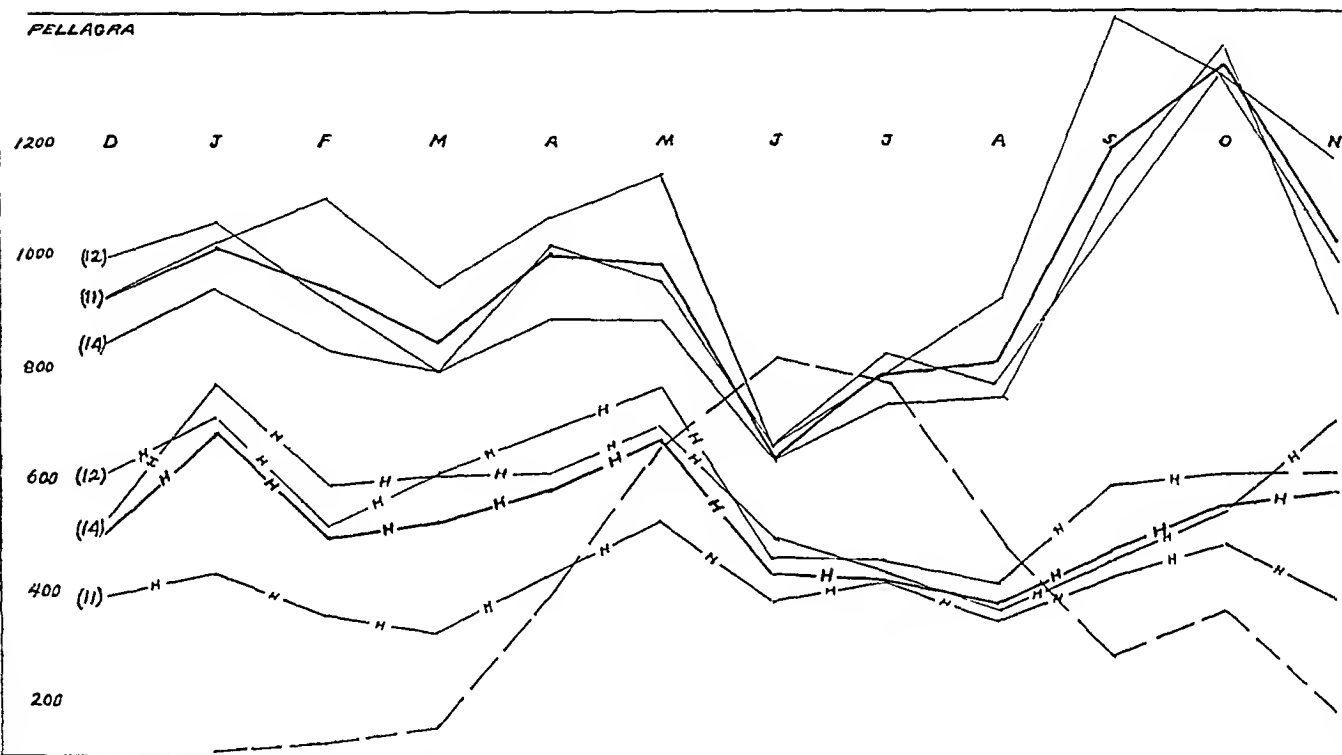


Chart 127 —South Carolina, 1927 Curve 11 indicates Charleston, 12, Columbia, 14, Greenville, the light continuous line, cloudiness, the heavy continuous line, the mean cloudiness, the light H line, the humidity, the heavy H line, the mean humidity, the broken line, the incidence of pellagra for the state

the warmest regions of the world, which are also characterized in general by excess wetness, live the rice-eating peoples" ⁴⁴

From what has been said with reference to the seasonal peak of the incidence of pellagra (June), the seasonal peak of the temperature (July or August) and the seasonal peak of humidity (August), it

* In certain sections of Florida, the culture of tobacco is carried on under cover (National Geographic Magazine, reference 75), implying a tropical solar radiation and heat somewhat unfavorable to the culture of tobacco. Possibly such conditions would also favor a high incidence of pellagra, but for the relatively high percentage of solar radiation throughout the winter (charts 9 and 23)

would appear that neither temperature nor humidity has a determining influence on the peak of pellagra. On the other hand, its general coincidence with the peak of solar radiation has been shown. With reference to this factor, it is to be noted that latitude 33° , the center of the pellagra belt in the United States, bisects the state of Mississippi. The supposedly protecting sun of winter swings lower for areas farther north, and the rays of the sun in summer are more direct on areas farther south, but this latitude represents the minimum of the first and the maximum of the second that is possible of combination (chart 10)

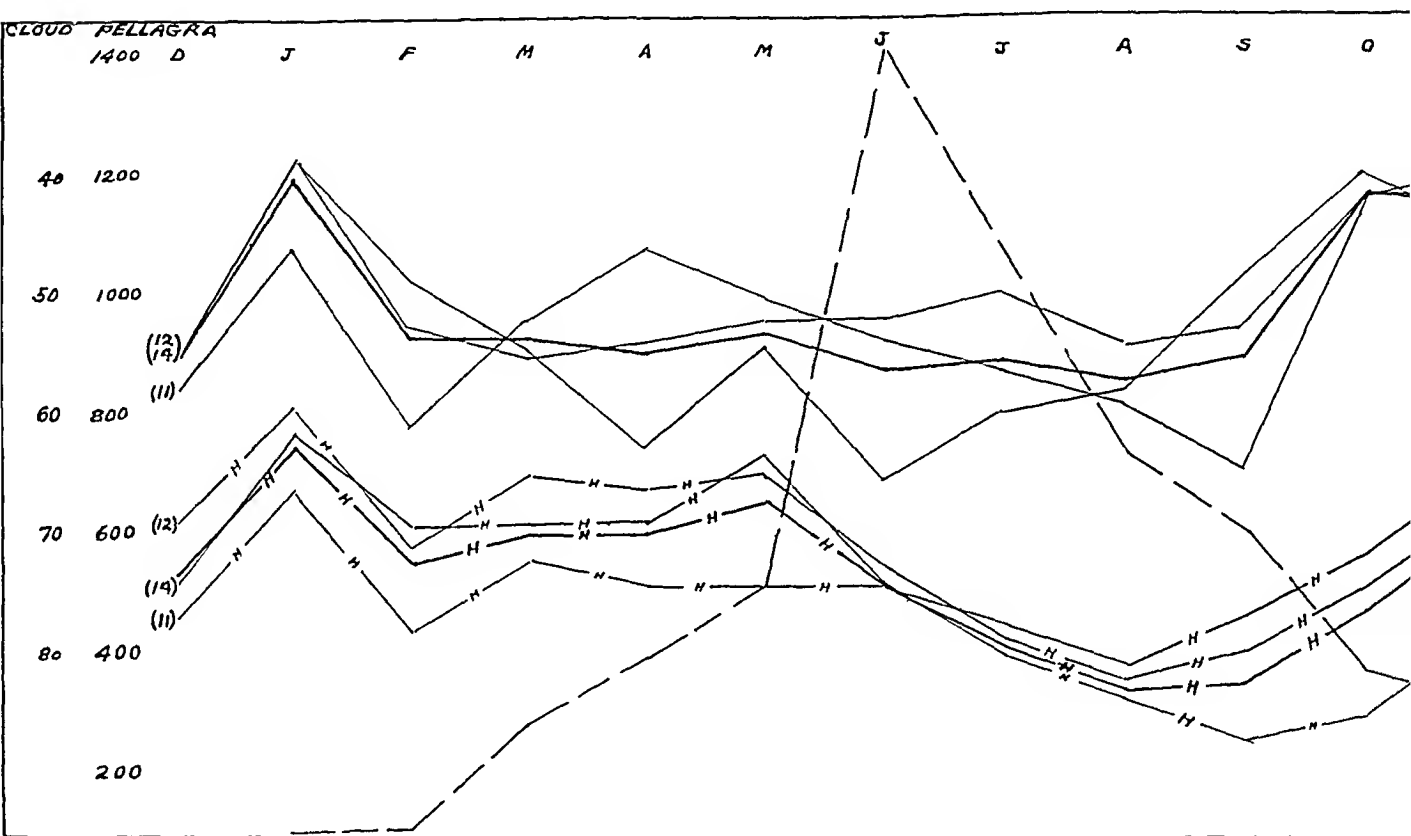


Chart 128—South Carolina, 1928. Curve 11 indicates Charleston, 12, Columbia, 14, Greenville, the light continuous line, the cloudiness, the heavy continuous line, the mean cloudiness, the light H line, the humidity, the dark H line, the mean humidity, the broken line, the incidence of pellagra for the state

Since the first census figures (1859), the centers of the production of cotton in the United States have remained within the borders of Mississippi (chart 131). This might not mean that the maximum production of cotton per square mile lies within the state, as centers to the east and to the west could give the same result, but actually as well as relatively it is the center, as is shown in table 22⁷⁴

If in the etiology of pellagra it is tentatively assumed that there is a genetic factor, it is to be noted that the foreign-born white population

is lowest in North Carolina (0.3 per cent) and is practically as low in Mississippi and South Carolina (0.4 per cent)¹⁰³ The Negro population may be considered to be practically all native born in the sense of southern born.

The liability of the Negro to pellagra is attested by various reports.³¹ Table 23 gives a report from the Board of Health for Mississippi.

The percentage of Negro population is highest in Mississippi (52.2 per cent) and next in South Carolina (51.4 per cent) (United States Census, Mississippi¹⁰³ and South Carolina¹⁰⁴).

As far as these figures go, the incidence of pellagra is higher but the mortality is conspicuously lower in the colored race than in the white race. According to Sullivan's classification, therefore, in the

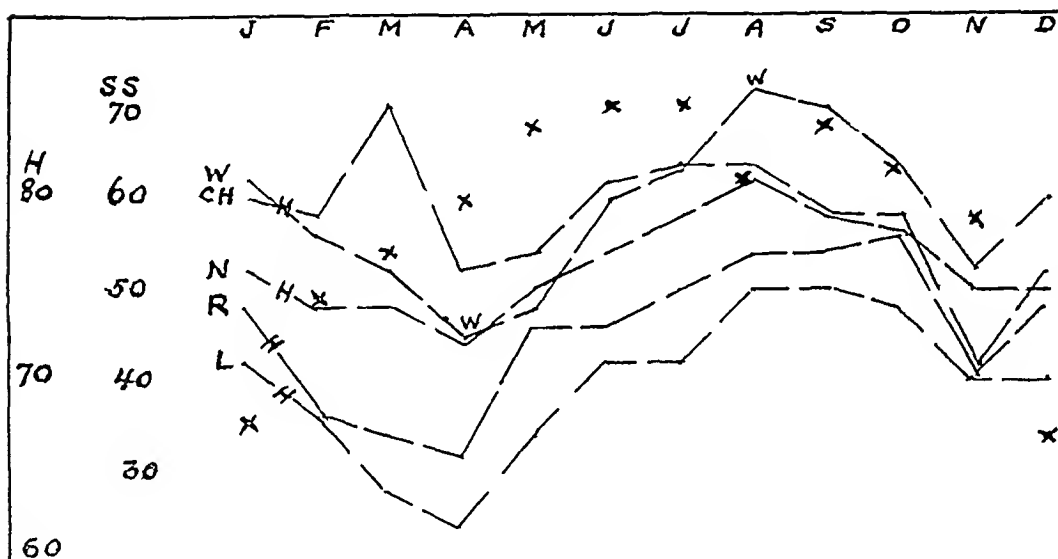


Chart 129—Virginia. X indicates the average sunshine at all stations, H, the average relative humidity, CH, Cape Henry, N, Norfolk, R, Richmond, L, Lynchburg, W, Wytheville.

Negro the disease would appear to tend toward the "dermal" rather than the "systemic" type.

As a probably valid index of economic disadvantage, it may be noted that the percentage of illiterate population 10 years of age and over was 21.9 for Louisiana, 18.1 for South Carolina and 17.2 for Mississippi, which compares with geographic divisions as follows: South Atlantic, 11.5, East South Central, 12.7 and West South Central, 10.¹⁰³

The studies of Vance¹¹⁰ and of others show that the prevalence of tenant farming in the cotton belt is an index of low economic status. In Mississippi, tenant farmers number 66.1 per cent of farms, in Georgia 66.6 per cent and in South Carolina 64.5 per cent, as compared with geographic divisions: South Atlantic, 46.8 per cent, East South Central, 49.7 per cent, and West South Central, 52.9 per cent.¹⁰³

As still another index applying more directly to food standards

The computed average for 1928 (of home-grown food used by the farm family) was highest for Arizona (\$399) and lowest for California (\$145). The average was \$389 for West Virginia, \$306 for Iowa, \$278 for Maine, \$244 for Arkansas, \$223 for Utah, and \$205 for Mississippi (1930) ¹⁰⁸

Chart 132 shows the density of population by counties in Mississippi, total and rural, which corresponds rather closely with the distribution

TABLE 22—*Production of Cotton in States Around Mississippi*

	Cotton, 1926, Running Bales	Square Miles per State, in Thousands	Bales per Square Mile, in Thousands
Alabama	1,470	51	29
Arkansas	1,513	53	28
Georgia	1,498	59	25
Louisiana	826	48	17
Mississippi	1,857	46	40
Missouri	215		
Oklahoma	1,760	70	25
South Carolina	1,025	30	34*
Tennessee	442	42	11
Texas	5,477	265	21
Virginia	51		
North Carolina	246	52	24

* With reference to these and other figures for Mississippi, it is of interest to note the corresponding figures for South Carolina, the second state in reported incidence in recent years

TABLE 23—*Liability of Negro to Pellagra*

	Pellagra, Incidence			
	1926	1927	1928	
White	2,363	3,491	3,667	9,521
Black	5,030	8,356	10,207	23,593
	<u>7,393</u>	<u>11,847</u>	<u>13,874</u>	<u>33,114</u>
	Pellagra, Deaths			
		1927	1928	
White		131	558	689
Black		99	648	747
		<u>230</u>	<u>1,206</u>	<u>1,436</u>

of pellagra. Chart 133 shows the percentage of Negroes in the total population, by counties, for this state ¹⁰³

Chart 134 shows the density of population, total and rural, by counties, in South Carolina ¹⁰⁴ (compare with chart 91, which shows the distribution of pellagra). Chart 135 shows the percentage of Negroes in the total population, by counties, for South Carolina ¹⁰⁴

In Mississippi,* it would appear that at least three factors probably contribute to the relatively high prevalence of pellagra, namely, its lati-

* There is reason to believe that the thoroughness of reporting in Mississippi is superior to that in other states and that this fact must be taken into account in any comparison of incidence, prevalence or distribution of pellagra

tudinal situation, the exposure incident to the planting of the high cotton acreage per square mile and the economic status of a portion of its population as indicated by illiteracy, tenant farming and direct statistical investigation

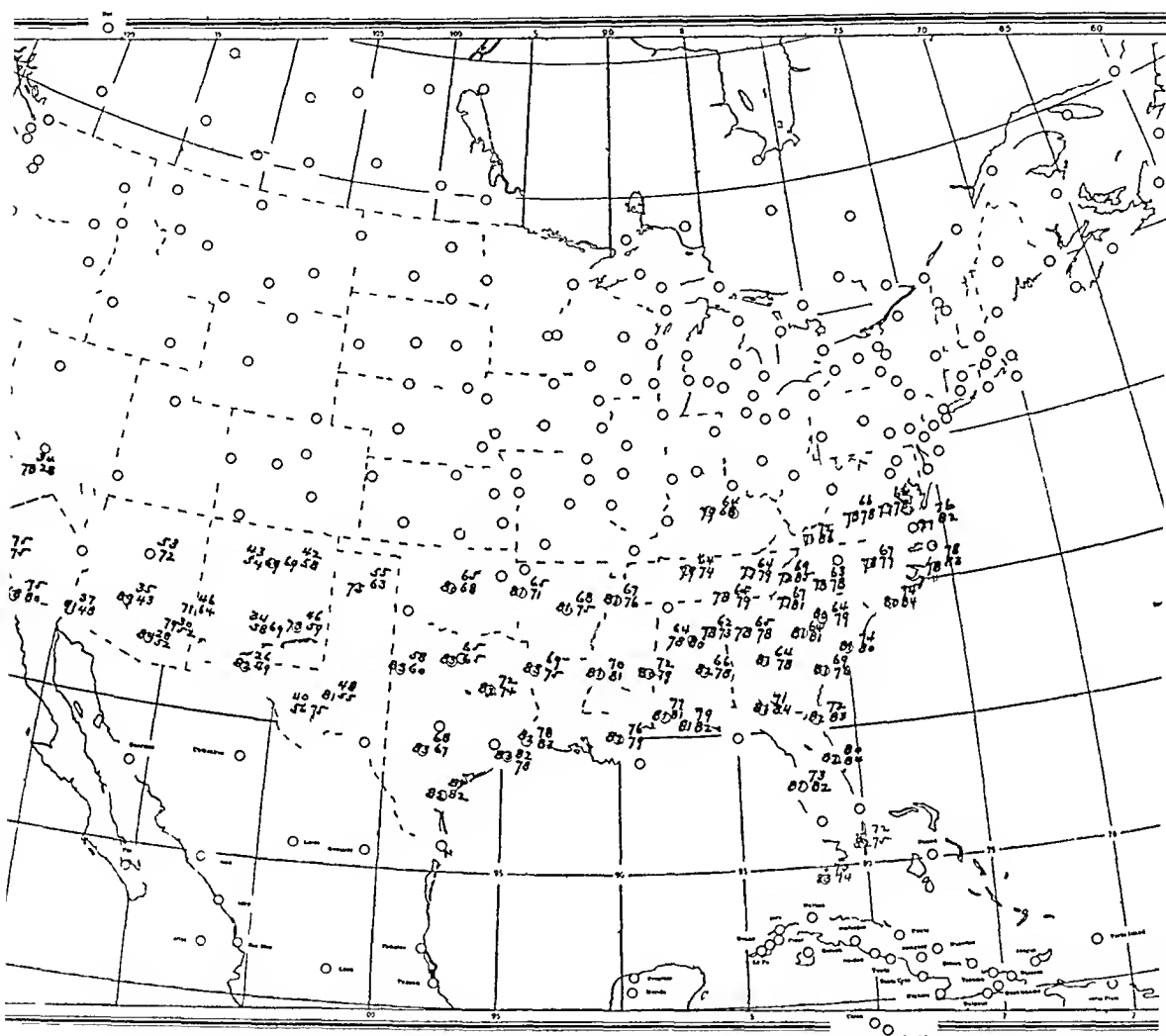


Chart 130—The light circles indicate the location of Weather Bureau Stations. The numerals, grouped in threes, represent the numeral on the left, mean temperature for July, the numerals on the right, mean relative humidity, above, for April, below, for August

THE INCIDENCE OF PELLAGRA IN WORKERS IN COTTON-MILLS

Generally speaking, pellagra is a disease of rural areas both in this country and in Europe. If there is an apparent inconsistency in attributing an etiologic influence to solar rays in two groups so differently situated as planters of cotton and tobacco on the one hand and workers in cotton-mills on the other hand, the explanation is considered to lie

in the feature of relative seasonal exposure, according to which the worker in the cotton-mill would seem to be exposed to the solar rays of summer of as great intensity and duration as the planter of cotton or tobacco in proportion to the respective amounts of solar radiation received by each group in winter

In general, it may be said that the pellagra zone begins where the zone of the siesta custom ends

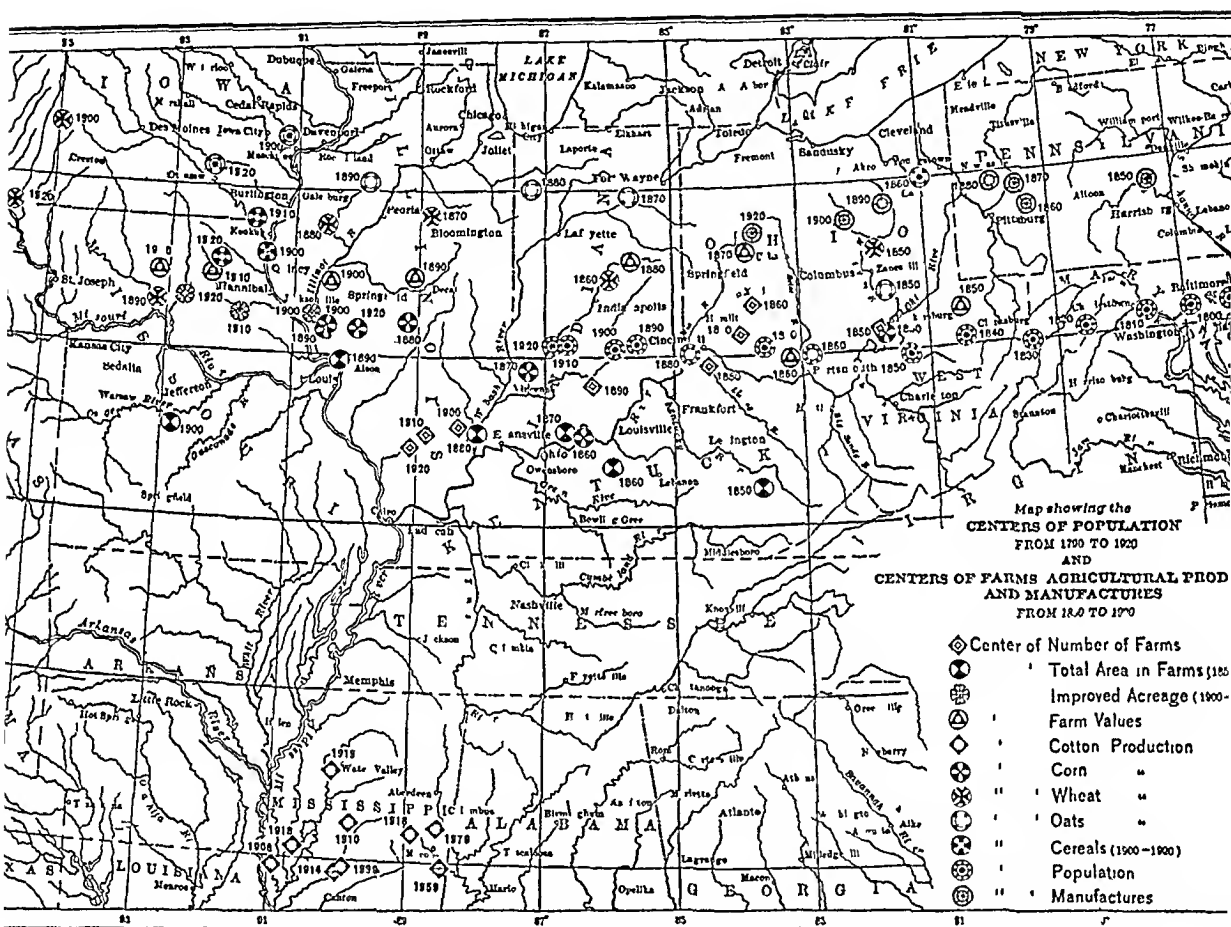


Chart 131—Map showing the centers of population and of production, including that of cotton, from 1859 to 1919 (From the Fourteenth Census of the United States)

If exposure to the inevitable lightly filtered solar rays of the summer season, even for irregular and brief intervals of the day and week, is deemed sufficient for the production of pellagra in the poorer classes subject to a deficiency of food, provided the deficit of sunshine in winter is relatively marked, these conditions appear to be met in workers in cotton-mills, who, as compared with the rural laborer, receive relatively little of the available sunshine in winter

The habits of the population in cotton-mill villages are described in the following note of the Hygienic Laboratory ⁴⁵

It was the custom in each community studied for nearly all able-bodied persons over 14, except farmers and housewives, to work for wages. In some villages many housewives worked in the mill, but, except in the cases of young married women without children, this was usually accomplished by hiring a Negro servant to care for the house and do the cooking (p 47)

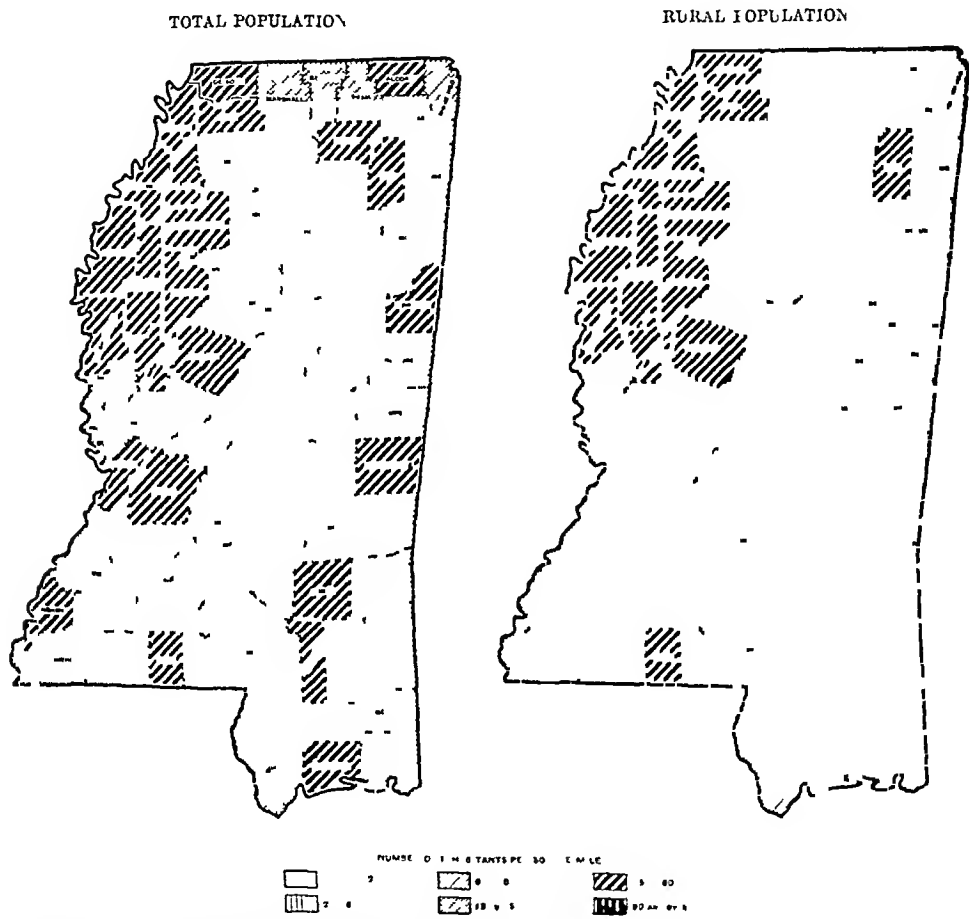


Chart 132—Density of the population of Mississippi, by counties, in 1920 (From the Fourteenth Census of the United States)

Rhynne ⁸¹ described the daily, weekly and annual routine of the cotton-mill worker and his economic and social status. Vance ¹¹⁰ gave these data as they apply to the “cropper” and tenant farmer and thus described the hereditary background, and of many the personal past, of the present-day worker in the cotton-mill

SUMMARY

It is believed that climatic factors are important in the causation of pellagra, and that the nutritional state of the individual conditions the reaction to the solar rays

Sulphur in the form of cystine appears to exert a protective action against exposure to solar radiation in low forms of life. Its high concentration in epidermal tissues of higher forms of animal life suggests a possible protective action in these animals also.

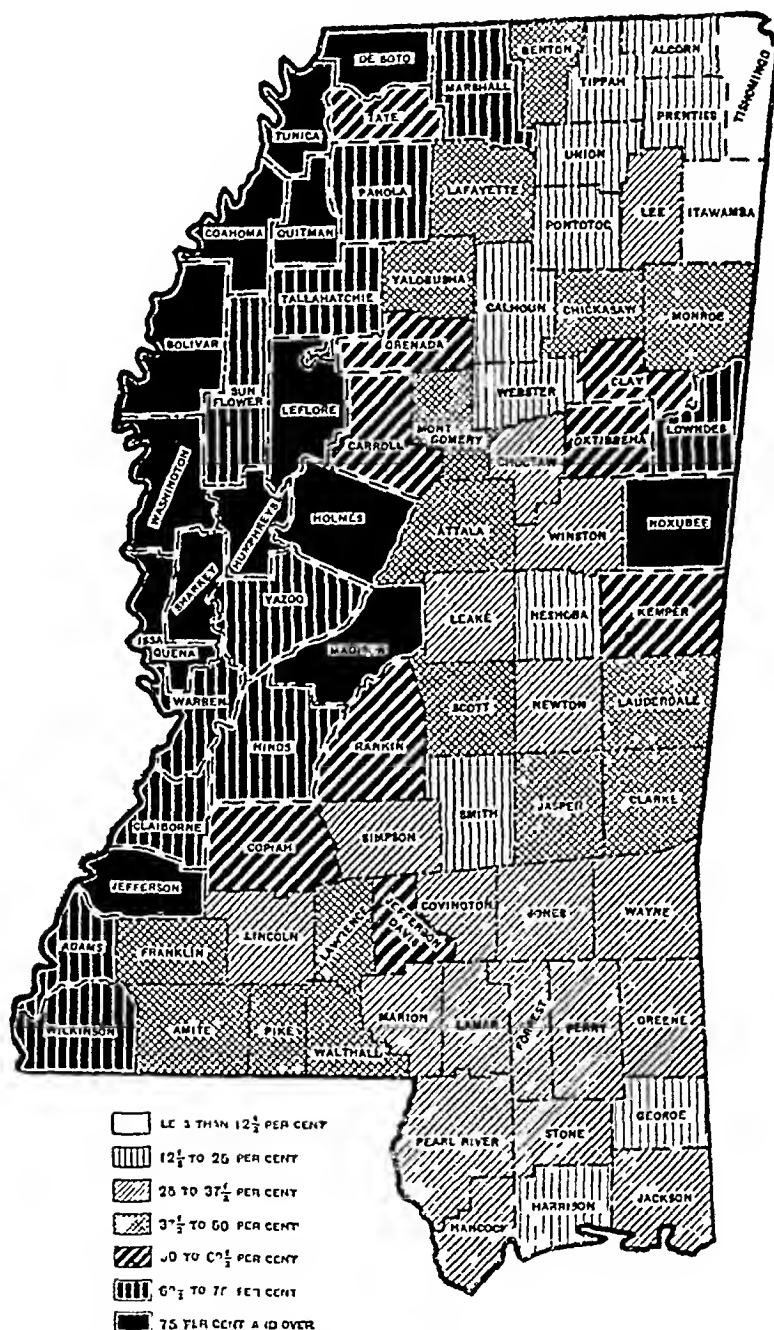


Chart 133—Percentage of Negroes in the total population, by counties, in Mississippi, in 1920 (From the Fourteenth Census of the United States)

There is evidence to suggest that an abnormal physiologic state of the lens of the eye with reference to the normal reversible cystine \rightleftharpoons cysteine reaction, together with exposure to ultraviolet wavelengths of light is important in the pathology of cataract. As an

illustration of the ideas developed, in this sense cataract may be thought of as pellagra of the lens

An initial disturbance of metabolism appears to result from a variation in the amount of radiant energy acting on the organism, whether the transition is from darkness to light or vice versa

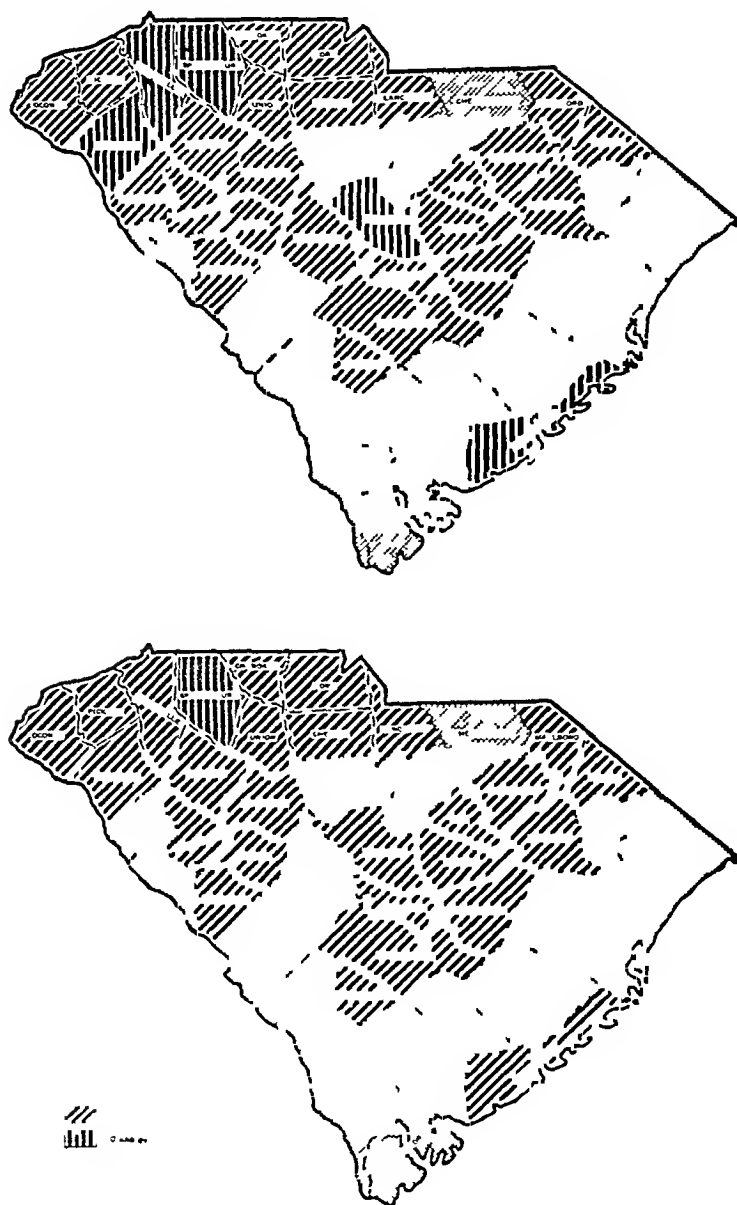


Chart 134—Density of the population of South Carolina, by counties, in 1920
Above, total population, below, rural population (From the Fourteenth Census of the United States)

In normal subjects, after ultraviolet irradiation, nitrogen equilibrium tends to be reestablished on a higher level than before, with retention of nitrogen. The disturbed metabolism of rats on a vitamin-free diet is "unable to stand the additional strain put upon it by radiation" (Eckstein)

Goldberger and Tanner thought that a deficiency of amino-acids was probably the primary etiologic factor in pellagra. The deficiency described by them was designated as a deficiency of the pellagra-preventive factor. It now appears that water-soluble vitamin B consists of at least two distinct factors, antineuritic and pellagra-preventive. These in combination, or possibly a third factor, represent the factor "bios," which is essential for the growth of animals.

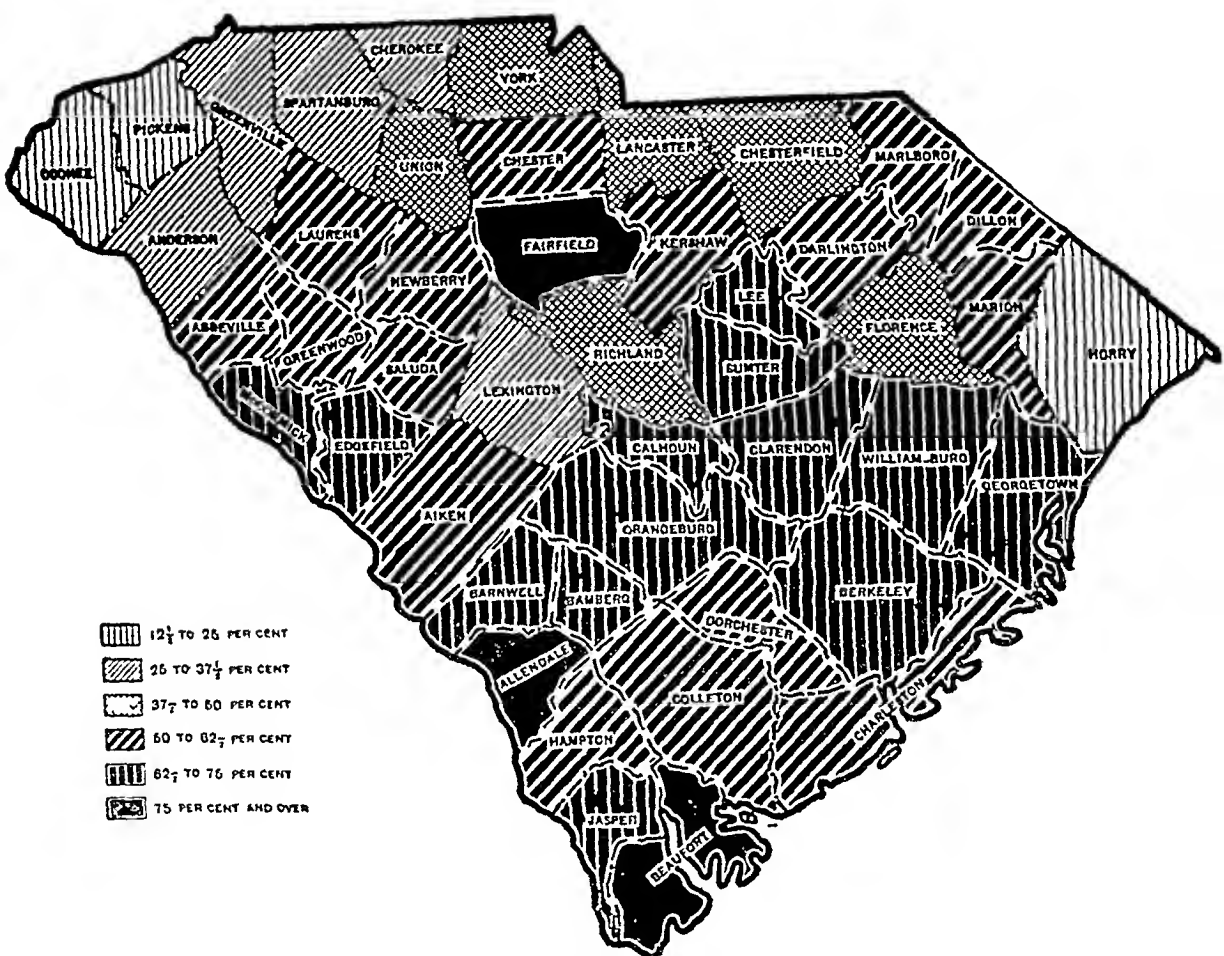


Chart 135—Percentage of Negroes in the total population, by counties, in South Carolina, in 1920 (From the Fourteenth Census of the United States)

A possible relation of a deficiency in supply or utilization of the sulphur-containing amino-acid cystine to the etiology of pellagra is more probable if it is assumed that solar radiation is also a factor in the etiology of pellagra. Cystine is protective against ultraviolet radiation. It promotes the growth of the yeast containing vitamin B. Its rôle is related to oxidative processes and to the detoxification of cyanogen compounds both of which functions are disturbed in pellagra. It is necessary to the growth and maintenance of animals and is important in the nuclear activity of cell division. It is the chief source of supply for the sulphur demands of the organism. After starvation the feeding

of an adequate diet results in the retention of sulphur. Glutathione (cystine in combination with glutamic acid) was originally isolated by Hopkins from yeast and from muscle and liver. The occurrence of cystine has been remarked in the foods that Goldberger and his associates advocate as preventive of pellagra, and they contain cystine (or sulphur) in proportions comparable to the value assigned by Goldberger in the prevention of pellagra. The evidence is suggestive that a lack of cystine may have a specific relation to the etiology of pellagra.

The protective value of pigment against the superficial effects of solar rays is a matter of common knowledge. Pigmentation is essentially the deposit of melanin, high in sulphur content. Pigmentation protects against sunburn, but not against pellagra. The cutaneous lesions of pellagra, while not limited to exposed areas, occur chiefly on exposed parts, and when exceptions occur the site of the exceptional lesion is usually on parts that phylogenetically may be considered exposed and related in function to a dissipation of heat by evaporation (the scrotum of man and the scrotum and tongue of dogs—black tongue).

The dermatitis of pellagra might conceivably be a local manifestation in the production of which exposure to solar rays was an important factor, and yet solar radiation might not have a relation to the deeper and more essential changes in the diseased tissues. That such is probably not the case is suggested by the fact that pigmentation does not protect against pellagra as it does against sunburn, by the greater mortality in the race (white) that is more susceptible to the erythematous effect of the sun's rays and should therefore more readily show mild forms of the disease, by the skepticism of experienced clinicians concerning pellagra *sine* pellagra and by the rarity of sore tongue, diarrhea and symptoms referable to central nerve changes in the absence of dermatitis. Laurens expressed the belief that "the only reasonable conclusion is that, following ultraviolet irradiation, some photochemical substance formed in the skin is carried by the blood stream to various organs, there bringing about the observed changes." In connection with commercial photography, Sheppard found that the photosensitivity substance of gels from animal hides lay in the doubly bonded sulphur as represented by allyl-isothiocyanate (mustard oil), in other words in sulphur as it occurs in cystine.

The sick organism is a much more delicate mechanism than the well, diseased tissue being more susceptible to radiation than normal (Laurens). "We may assume that normal tissue acts like a slow (photographic) plate and diseased tissue like a fast one" (Clark). These are doubtless important considerations in connection with the known fact that the sites of predilection for the cutaneous lesions of pellagra are exposed surfaces.

The theory of a deficiency of food as the cause of pellagra and a relation between this deficiency and the economic status seem to be well established principles in the etiology of pellagra. A specific deficiency may be involved, such as of amino-acids, and possibly cystine, but this does not rule out the rôle played by the level of basal metabolism, which in turn may be influenced by a lowered intake of protein and a corresponding reduction in the "specific dynamic action" of the ingested food. Further, the intensity of the solar radiation may play a part in the etiology of pellagra through a lowered intake of protein, a direct effect on the general level of metabolism or a specific metabolic influence, such as an altered metabolism of cholesterol, nitrogen or sulphur, and the effect of a given intensity of solar radiation may depend on other factors, such as the nutritive state of the subject and variation from the intensity of recent previous exposure to solar rays.

When viewed with special reference to sulphur metabolism, the chemical analysis of pellagra may begin with the suggestion of Sullivan and his co-workers, in 1919 and 1920, that sulphur metabolism in pellagra is abnormal. The restoration of a normal exogenous sulphur (and nitrogen) metabolism in the patient who has recently had pellagra is not immediately accompanied by restoration of a normal endogenous sulphur (and nitrogen) metabolism. The excretion of thiocyanate in the urine and saliva is decreased, as is the excretion of creatinine in the urine, but Voegtlin found neutral (unoxidized) sulphur increased in the urine. In the central nervous system a loss of neutral sulphur in the cerebrum and spinal cord is described by Koch and Voegtlin, together with an increase of this constituent in the cerebellum. The various observations quoted indicate at least an abnormality of sulphur metabolism in pellagra. While the general depression of oxidative processes in pellagra may not be related to sulphur metabolism (glutathione), Bodansky and Levy found that an adequate supply of cystine was necessary to maintain an unimpaired cyanide-detoxifying power in the pellagrin.

Hypochlorhydria is usual in pellagra, and achlorhydria with an absence of pepsin is common. Pepsin apparently is necessary for the digestive alteration of the protein molecule so as to produce a nitroprusside reaction. Abderhalden suggested that pepsin and trypsin affect the molecule of albumin at different parts and that pepsin probably splits the S-S compound by forming groups of SH, SH.

In Goldberger and Wheeler's experimental pellagra in white male convicts, the relative influence of diet and solar light was apparently not taken into account. The lesions of the skin appeared primarily and chiefly on the scrotum, and Goldberger and Wheeler suggested that the site of at least the initial dermatitis is bound up with a specific quality

of diet If both dietary deficiency and exposure to solar rays are usual factors in the etiology of spontaneously developing pellagra, Goldberger and Wheeler's data suggest that the results obtained by them represented an instance of exaggerated dietary influence as compared with the influence of solar light, and it would be suggested as a possibility that this imbalance in causation determined the site of the major lesions of the skin on the heavily pigmented, unexposed genitals, highly endowed as to function for the loss of heat through evaporation

Goldberger and Wheeler hold that black tongue in the dog is the analog of pellagra in the human subject Observations similar to those just made with reference to their experimentally produced pellagra seem appropriate in connection with their experimental black tongue, emphasized somewhat by the fact that the scrotal lesions experimentally produced in dogs have never been recorded in the spontaneously developing disease The heat-dissipating function of the dog's tongue, the usual site of conspicuous lesions in black tongue, is well known and seems to represent an analog in the functional sense to the skin of the human subject

A series of three comparisons is made as follows (1) spontaneous pellagra and Goldberger's convicts, (2) spontaneous black tongue and Goldberger's dogs and (3) Enright's Germans and Bigland's Ottomans, prisoners of war in Egypt In each of the three comparisons it would seem that when dietary deficiency is obvious and outstanding (the second instance in each group) in comparison with exposure to light, the effect partakes of a general or systemic reaction or type (defined by Sullivan as "systemic" as opposed to a "dermal" type in which the cutaneous lesions are relatively conspicuous), dermal effects readily attributable to direct exposure to light are at a minimum, scrotal lesions are relatively high, and mortality, when it can be compared, is great

Koch and Voegtlin carried out experiments on rats and monkeys, observing the chemical and histologic changes in the central nervous system as a result of a restricted vegetable diet They noted that, in general, the changes observed, including their studies of the sulphur fractions, corresponded somewhat closely to those observed in pellagra While the authors did not ascribe a significance to the influence of sunlight, their tables clearly show the extent of exposure of the monkeys to sunlight and appear to warrant the notation of an inverse correlation between the hours of exposure and the duration of life and a critical influence of short exposures following dietary restriction and previous exposure to sunlight

Analysis of the age and sex incidence of pellagra reveals a striking direct correlation with the age period and sex of child-bearing On

the other hand, at either extreme of life the incidence tends to be somewhat higher in the male, possibly being associated with his more exposed outdoor life

A curious parallel is noted between the age and sex incidence of pellagra and the tendency to excrete creatine in the urine. Characteristic of children of both sexes, the male ceases to show the tendency early, while the female, during pregnancy and in an intermittent fashion probably related to the menstrual cycle, continues to excrete creatine. In the adult male, creatinuria is rather a phenomenon of starvation or disease, especially of muscular dystrophies. In general, creatinuria appears to be indicative of a departure from the relative fixed and stable metabolism of the normal adult male. Hunter stated that "the avidity of the muscle for creatine and its efficiency as a machine develop together, and as they develop, creatine disappears from the urine." Harding and Young suggested that creatine is a derivative of cystine. In this sense, creatinuria would be regarded as a departure from the normal metabolism of cystine in the adult male. At least it is known that during pregnancy there are large positive gains in the storage of sulphur. Koch and Voegtlin reported that from infancy to maturity a shift takes place in the sulphur fractions in the central nervous system, with a decrease in neutral sulphur in favor of protein sulphur. The age and sex incidence of pellagra affords interesting parallels with certain features of metabolism, but the significance of those referred to is far from clear.

The geographic distribution of pellagra is limited rather closely to the isothermal line of 80 F average July (in the northern hemisphere) temperature, and the areas along this line where pellagra is endemic, generally speaking, are also in an isothermal belt of from 40 to 50 F average January (in the northern hemisphere) temperature. However, any influence that this characteristic climatic feature has may not be essentially thermal, but may be mediated through such secondary features as the ultraviolet wavelength content of the solar rays or the determining influence of the climate on agriculture.

Certain features of the physics of light have been reviewed with special reference to ultraviolet wavelengths. Actual measurements of seasonal variations in intensity, as reported (chart 13), conform quite closely to a curve representing the seasonal variation in the air mass traversed by the solar rays at the corresponding latitude (in the north temperate zone) (chart 10). With the air mass held constant, pyrheliometric measurements at Naples and Florence, Italy, show that at Naples (a nonpellagrous area) the heat intensity of the solar rays is highest in winter, thus tending to offset the increased filter thickness of the air mass in winter and, therefore, to equalize the exposure to the solar rays

throughout the annual cycle At Florence (located toward the pellagra area), with the air mass held constant, the seasonal variations in the intensity of heat tend to conform to the variations dependent on the air mass (greatest in summer), thus tending to an exaggeration in the degree of variation in the intensity of the solar rays in summer as compared with that in winter An erythema effect of ultraviolet rays is well established Tisdall and Brown have furnished experimental evidence of maximal diurnal and seasonal variations in the antirachitic effect of ultraviolet solar rays

The data at hand suggest that there are seasonal variations in the average basal metabolism of the population of a given area, but that these seasonal variations are not the same for different latitudinal belts in the same hemisphere

In the far north, metabolism seems to be lowest in winter

In the tropics, there is no evidence of any marked seasonal variation, and there is no marked seasonal variation in this part of the earth's relation to the sun

In the latitude of the southern United States, metabolism seems to be lowest in summer, and the curve of average metabolism seems to be roughly in direct relation to the curve of the air filter, with certain departures, as in August, to correspond with variations in water vapor (chart 22)

In the latitude of Boston and Chicago, the data are conflicting, but taken as a whole they might be considered consistent as a latitudinal group if there is actually a reversal in the season peaks, respectively, in latitudes farther north and farther south, as the present data seem to suggest

A constantly lower level of metabolism is probably characteristic of warm climates as compared with cold climates Almeida suggested that in sufficient time all the factors which modify the total metabolism will finally alter the value of the basal metabolism This idea leads to the consideration of a hereditary level of metabolism or a genetic factor affecting the habitual rate and its possible bearing on the development of pellagra

According to Laurens' suggestion that the metabolic effects of ultraviolet radiation are of greatest significance when taken into consideration with the accustomed exposure to these rays, the stationary population of any area is subject to deviation in at least three ways in the amount of radiation received from the sun (1) variation in the altitude of the sun and the thickness of the air filter (annual regularity and seasonal variation), (2) variation in cloudiness (annual irregularity and seasonal irregularity) and (3) variation in exposure to the available sun in winter and to the inevitable sun in summer (annual irregularity and seasonal irregularity)

Examination of the distribution of pellagra in the United States with reference to the idea of a determining influence of the relation between maximum and minimum exposure to solar rays during the annual cycle (under certain abnormal conditions of nutrition) appears to indicate that, so far as the sun's angle is concerned, solar rays have a pellagra-producing effect in areas receiving them at an angle of $75^{\circ} 30'$ or above, but in view of the relatively low prevalence of the disease in the tropics, a more efficient pellagra-preventive effect would be attributed to solar rays reaching the earth's surface at no time of the year below an angle of $38^{\circ} 30'$

With further reference to a protective influence of winter sunshine within the pellagra belt in the United States, in areas where there is no deficit of winter sunshine below 70 per cent of the possible sunshine (longitude, from 101° to 105° W), pellagra is not prevalent, where there is a slight deficit below 70 per cent but not as much as 10 per cent (Florida and California), there were less than 100 cases of pellagra per state reported in any year from 1926 to 1928, inclusive, and in areas in which there was a deficit of winter sunshine of from 10 to 27 per cent below the standard of 70 per cent (from the Atlantic coast to longitude 101° W), there were 500 or more cases of pellagra per state for each of the three years (chart 23)

Examination of the seasonal incidence of pellagra in nine southern states revealed a marked tendency for the curve of the incidence of pellagra to rise and fall with the decreasing and increasing air filter (chart 51), if the curve of ultraviolet intensity at Davos, Switzerland (chart 13), is considered as applicable to these states, the tendency is for the seasonal incidence of pellagra to rise and fall with increasing and decreasing intensity of ultraviolet radiation, or, if the curve tentatively presented as that of the average basal metabolism in Virginia (chart 22) is considered as applicable generally to the southern United States, the tendency is for the seasonal incidence of pellagra to rise and fall in the direction opposite to the rise and fall of the average basal metabolism. The larger the number of cases of pellagra in a given state for a given year, the closer these parallels tend to be. Therefore, the peak of the incidence of pellagra is usually near the summer solstice. The month of the peak may follow the summer solstice or it may precede it, but as far as the observations go, it does not precede the peak of sunshine or the absence of cloudiness so far as this peak occurs prior to the summer solstice.

A secondary rise or peak following the summer solstice is not seen save when there is a corresponding absence of cloudiness or a relative rise in the percentage of sunshine. In general, the curve for pellagra deviates from that for the air filter to correspond with that for excess

sunshine (chart 49) Doubtless in August as many persons have a tissue metabolism favorable to the development of pellagra as in either July or September, but lack whatever influence there may be in a relatively greater solar radiation

The clinical progress of the disease is generally similar to the curve of incidence—spring onset, summer exacerbation and improvement in the fall and winter The decline of the season of prevalence sets in only after the advent of a decline of the sun toward the south

The distribution of pellagra in the southern part of the United States appears to be closely correlated with the distribution of the planting of cotton and tobacco, more generally cotton (charts 103 and 104) At least three possible explanations may be considered These crops are planted at or near the summer solstice The states in which these pursuits are followed are numbered among the states with the lowest average income per farm The planting of any crop on a large scale tends to reduce the production of other crops and in this instance tends to crowd out the raising of foodstuffs

With reference to variations in the annual incidence of pellagra in a given state or county, there are data to suggest that high winter cloudiness (low percentage of the possible sunshine) and high November sunshine (low percentage of cloudiness) tend to an increased incidence of pellagra during the following year Both of these conditions involve deviation from a standard annual exposure to solar rays There are also data to suggest that an increased cotton or tobacco acreage tends to an increase in the incidence of pellagra, though this factor (regarded here as climatic, involving exposure to the solar rays of summer) appears at times, indeed usually, to have an inherent offset in itself by reason of its contribution to the value of the crop (regarded as an economic index tending to influence nutrition)

Still another factor that appears to influence the incidence of pellagra in a given year is the incidence in the same area during the previous six or twelve months Whatever may be the conditions favorable to a high incidence of pellagra, it would seem to be a reasonable assumption that conditions operating broadly to produce a high incidence in any given year would tend to affect an indefinite number of persons who, whether the disease did or did not develop in them during the current year, would be somewhat more liable to the disease the following year than would have been the case had the conditions of the current year been less favorable to a high incidence Statistically, there is valid objection to considering along with supposed etiologic factors one expression of the incidence of pellagra when the effect under consideration is another expression of this incidence This objection is regarded as somewhat less valid in view of the tendency for the incidence of pellagra to approach zero in the winter

As indexes of the economic status of the population planting cotton (and tobacco), the production of cotton (acreage multiplied by yield per acre) and the price of cotton realized by the farmer have been used in comparison with annual variations in the incidence of pellagra. At times, the correlation appears to be quite close, and in general it is suggestive of a relationship of depressed economic conditions to the incidence of pellagra.

A division of the year into first and second halves appears to favor correlation of the several factors mentioned with the incidence of pellagra in corresponding periods of time. When all the data are considered, the correlation between the incidence of pellagra and the several factors combined (climatic, economic and "momentum") appears to be closer than the correlation between any one or any more limited combination of these factors (charts 116 and 117).

Unusual conditions, such as the flood in the Mississippi Valley area in 1927, appear to influence the correlation of the incidence of pellagra with factors considered as climatic—winter cloudiness and cotton planting—the latter, through delay in planting, tending to an increased incidence in the latter half of the year. It seems probable also that such a disaster would influence the incidence through economic stress and nutritional lack, as was anticipated and positively regarded by the United States Public Health Service.

There is not an apparent relation of temperature and humidity to the geographic distribution and prevalence of pellagra further than that in general, in the pellagra belt, temperature and humidity approximate the levels described by various authors as favorable to a minimum metabolism and to a low intake of protein.

Coastal areas appear to be relatively free from pellagra (chart 103). This may be due to certain known climatic features, to certain known differences in agricultural pursuits as compared with more inland areas or to other and unknown factors.

The highest reported incidence of pellagra in the United States is in Mississippi. In addition to superior thoroughness in reporting, at least three factors would appear to be contributory to a relatively high incidence in this state, namely, its latitudinal situation that results in the maximum of summer directness and the maximum of winter obliquity of solar rays that is possible of combination, its high cotton acreage per square mile (in excess of all other states) and the economic status of a portion of its population, as indicated by illiteracy, tenant farming and the computed average of food used by the families on the farms.

In a study of the incidence of pellagra in cotton-mill villages in South Carolina, the Hygienic Laboratory found evidence of

economic fluctuations apparently conditioning the nutritive state of the population. In addition, if exposure to the inevitable lightly filtered solar rays of the period of the summer solstice, even for irregular and brief intervals of the day and week, is deemed sufficient for the production of pellagra in the classes of population subject to a deficiency of food, provided the deficit of winter sunshine is relatively marked, these conditions appear to be met in workers in cotton-mills who, as compared with the rural laborer, receive relatively little of the available winter sunshine.

There may be significance in the fact that the pellagra zone begins where the zone of the siesta custom ends.

In general, this study is intended as a basis for further experimental work and as a basis for contemporary observation as suggested by analysis of past events. However, under controlled experimentation and observation with a limited number of subjects, there would remain the possibility that the sampling or selection of subjects failed to take into account some undetermined factor of individual metabolism present in some but not in others of the general population and conditioning the end-result. Such an explanation may account for the fact that a condition that was considered to be pellagra developed in only six of Goldberger and Wheeler's subjects used for experimentation.

CONCLUSIONS

That there are biologic effects due to radiant energy is not open to question, and that some of these are related to pellagra seems probable.

An adequate supply and a normal metabolism of sulphur appear to exert a protective influence against the pathologic effects of solar irradiation. The evidence suggests that an inadequate supply of sulphur as cystine is an important cause of pellagra, and that the abnormal metabolism of sulphur is an important feature of pellagra.

The distribution of pellagra and the variations in its prevalence and incidence suggest that solar irradiation, under certain abnormal conditions of nutrition, is an important factor in the etiology of pellagra, and that the reaction to solar rays not only is conditioned by the nutritive state, but depends on a state of the tissues determined by contrasts in degree and intensity of exposure during the annual cycle.

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SYMPATHETIC ACTIVITY IN CERTAIN DISEASES, ESPECIALLY THOSE OF THE PERIPHERAL CIRCULATION *

W J MERLE SCOTT, M D

AND

JOHN J MORTON, M D

ROCHESTER, N Y

Fundamental facts concerning the anatomy and the physiology of the sympathetic nervous system lay dormant for many decades. At the end of the nineteenth century, several attempts were made to influence the course of epilepsy, exophthalmic goiter and glaucoma by interrupting or excising parts of the cervical sympathetic chain. These efforts had been almost forgotten, owing to the poor results achieved, when, in 1916, Jonnesco attracted the attention of the medical world by performing cervical sympathectomy for angina pectoris. The interest in the removal of the sympathetic influence was greatly quickened by Leriche's work on periarterial sympathectomy, which he first employed in 1917 in the treatment for causalgia and in subsequent years for other conditions attributed to vasomotor disturbances. The eradication of visceral pain by interrupting sympathetic impulses, either temporarily as a diagnostic measure or permanently at operation, further attracted attention in recent years to this system. This interest, however, has been greatly stimulated since the work of Hunter and Royle in 1924. This episode illustrates excellently the value of painstaking clinical observation. After a great deal of clinical and experimental work, there is still much doubt concerning the major point of their investigation, namely, the influence of sympathetic impulses on muscular spasticity. But two of their incidental observations have opened up important lines of attack in fields quite unrelated to that of their primary objective. Hunter and Royle noted that the obstinate constipation shown by several of their spastic paralytic patients was overcome after lumbar sympathetic ramisection, and also that the foot on the side on

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which operation was performed became much warmer. Operations to interrupt the lumbar sympathetic nerves were then undertaken as empiric procedures by various surgeons in thrombo-angitis obliterans, Raynaud's disease and Hirschsprung's disease. Dr. Elliott C. Cutler and one of us (Dr. Scott) performed lumbar sympathetic ganglionectomy in two cases of thrombo-angitis obliterans a few weeks after the visit of Hunter and Royle to this country in 1924. These patients were selected as their symptoms seemed to afford a good basis on which to judge improvement. Both had severe, almost unbearable, nocturnal pain, with the usual manifestations of greatly impaired circulation in the foot. In one case, a large and slowly progressing ulcer on the dorsum of the foot was evidence of serious circulatory deficiency. This patient showed no benefit from sympathectomy and required amputation soon afterward. The other patient showed definite clinical improvement, the paroxysms of excruciating pain were almost entirely controlled, and a gangrenous area on one toe slowly healed. He was able to use his foot for several months, but returned within a year with further gangrene, for which amputation was done. From results of sympathetic interruption reported in the literature, it soon became apparent that some benefit was being achieved in certain cases, while in others the operation failed to affect the disease materially. In fact, this pioneer work has indicated a number of pathologic fields in which sympathetic activity may play a leading rôle in the production of harmful effects. From the first, however, an important obstacle to the clinical exploitation of these possibilities has been the lack of accurate criteria by which to demonstrate and to measure the element of sympathetic activity in the clinical syndromes.

In 1929, this need presented itself to us in deciding on the treatment of a patient with a typical example of Hirschsprung's disease. At that time, the results of interrupting the sympathetic innervation of the large intestine for this condition were recorded in the literature in only seven cases. In five of these, the immediate result was distinctly gratifying although the interval of postoperative observation was too short to warrant final conclusions. If sympathectomy would cure this patient, we surely wanted to carry it out. On the other hand, if it would not benefit this particular child, we did not want to submit him to the operation unnecessarily. We reasoned that if the abnormality was dependent on activity of the lumbar sympathetic nerves and would be benefited by their removal, then temporary improvement in the motility of the bowel should be demonstrable after the lumbar efferent sympathetic fibers from the cord were paralyzed. Consequently, we determined the motor function of the bowel by a barium enema before and

after the induction of spinal anesthesia¹ The effect of this procedure was so striking that we were convinced that the patient would be greatly benefited by permanent interruption of the lumbar sympathetic outflow After bilateral lumbar sympathetic ganglionectomy, the patient began to have regular bowel movements and became capable of completely emptying the contents of the left colon, as demonstrated by a motor test with a barium enema We have applied this method, with similar convincing results, in another case of Hirschsprung's disease This procedure has also shown its value in two cases of obstinate constipation not of the Hirschsprung type The latter patients did not show the rapid emptying of the distended bowel after spinal anesthesia that the former did We concluded, therefore, that the constipation arose on some basis other than sympathetic activity, and that sympathectomy would not relieve their obstipation In order to demonstrate further the effect of spinal anesthesia on the motor mechanism of the large bowel, this was studied in the cat Under the conditions of the experiment, with the animals under light ether anesthesia, the straight intestine was exposed and kept moist with a fine saline spray, it showed no effective peristaltic or expulsive action, even when fully distended with fluid Shortly after the introduction of procaine hydrochloride intraspinally, vigorous coordinated peristalsis appeared, first in the cecal region, followed in a short time by powerful expulsive contractions, resulting in the emptying of the bowel when it was distended From this clinical and experimental work, we concluded that spinal anesthesia was a satisfactory method for testing the presence of sympathetic inhibition acting on the large bowel It also seemed reasonable to expect that this method would prove equally effective in connection with other symptoms under the influence of these nerves We turned our attention, therefore, to its application in diseases of the peripheral vascular system

PERIPHERAL VASCULAR DISEASE

REVIEW OF THE LITERATURE

"In those cases of gangrene in which no obstruction has been found after death in the vessels of the dead parts, it is extremely probable that a long persistent spasm of the blood vessels has existed" Thus Brown-Séguard,² in a lecture before the Royal College of Surgeons of

1 Roentgenograms of this procedure will be found reproduced in one of our previous papers Scott, W J M, and Morton, J J Sympathetic Inhibition of the Large Intestine in Hirschsprung's Disease, *J Clin Investigation* 9 247, 1930

2 Brown-Séguard, C E Course of Lectures on the Physiology and Pathology of the Central Nervous System Delivered at the Royal College of Surgeons of England in May, 1858, Philadelphia, 1873, p 148

England in May, 1858, called attention to the clinical importance of vascular spasm and its differentiation from occlusion. In the early part of the same decade, Claude Bernard had demonstrated the vasoconstrictor fibers in the cervical sympathetic chain. The physiologic action and anatomic pathways of the sympathetic vasoconstrictors are well known. This information, however, has not been applied to the development of a practical method for differentiating the elements of spasm and occlusion, and for determining their relative participation in any individual case of peripheral vascular disease. As will appear later, this distinction is of great significance in the common forms of vascular disease, not merely in the unusual instances, such as those alluded to by Brown-Sequard and those described by Raynaud, in 1862, in his classic monograph on local asphyxia and symmetrical gangrene of the extremities. French investigators,³ by the use of the oscillometer before and after immersing the extremity in a hot water bath, had attempted this distinction. However, this method gave no index to the blood flow through the finer vessels of the collateral and terminal circulation. It is inadequate for our purposes. The hyperthermia following the parenteral administration of a foreign protein had long ago been advised as a method of treatment in many conditions, among them the peripheral vascular diseases. Brown⁴ applied this reaction to the diagnosis of these peripheral vascular diseases, deriving a vasomotor index from a comparison of the increase in surface temperature of the foot with the increase in body temperature. This method offered the first differentiation of spasm and occlusion in the involved area. We have used it several times, but it is disagreeable to the patients and inconvenient to the physician, and in some reported cases⁵ has resulted in serious complications. Consequently, we applied ourselves to the development of a simpler procedure to measure the elements of spasm and occlusion in the extremity. It was an obvious step to carry out the same procedure in vascular disease that had been so satisfactory as a test for sympathetic activity in Hirschsprung's disease. We therefore studied the effect of spinal anesthesia on the circulation through the extremities in persons with normal vascular systems as a basis on which to interpret the response in pathologic cases.

3 Babinski, J, and Heitz, J. Obliterations artérielles et troubles vasomoteurs d'origine réflex ou centrale, *Bull et mem Soc méd d hôp de Paris* **40** 570, 1916.

4 Brown, G. E. The Treatment of Peripheral Vascular Disturbances of the Extremities, *J. A. M. A.* **87** 379 (Aug 7) 1926.

5 Allen, A. W., and Smithwick, R. H. Thrombosis of Peripheral Arteries Following Intravenous Injection of Typhoid Vaccine. Report of Two Cases, *New England J. Med.* **200** 217, 1929.

METHODS OF MEASURING VASOMOTOR CHANGES IN THE EXTREMITIES

Let us interpose here a few remarks about the method chosen to measure the vasomotor changes in the extremities. Three such methods are available and have been used in studying the peripheral circulation in the laboratory and in the clinic. These are (1) plethysmographic records of volume changes, (2) determination of the rate of dissipation of heat from the part, usually by a water calorimeter, and (3) determinations of the surface temperature. The plethysmographic and calorimetric methods, though sensitive indexes of the rate of blood flow are not applicable to comparative determinations in various areas, such as the different toes, or the toe as compared with the sole, etc., data that, as will appear later, are of importance to us. They are available for

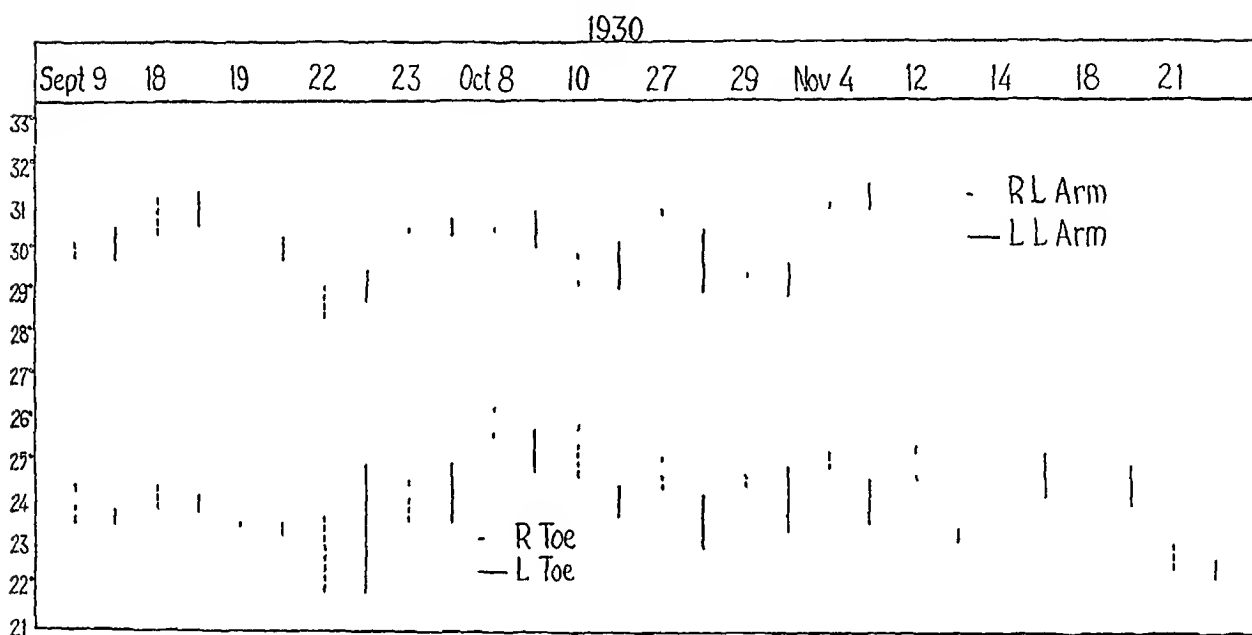


Fig 1—Skin temperature variations of a normal subject (Miss O. E.) in a room at a constant temperature (20 C [68 F]). Each line represents the maximum and minimum readings over a period of one-half hour. The area of skin was exposed to the standard conditions for fifteen minutes each time before temperature readings were started.

clinical use only when applied to larger parts, such as the whole foot or lower part of the leg. The surface temperature, however, can be easily and quickly determined for any number of points. At a given room temperature, it is an accurate index of the blood flow through the involved area, if this does not closely overlie contracting muscles. In normal persons surface temperatures vary greatly (fig 1). What, then, is their significance, and how are they of use to us in studying the present problem? The actual reading at which the surface temperature starts is of little significance. It is an index of the arteriolar circulation, which is undergoing many physiologic changes during the day under normal conditions, as is well known. Comparative temperatures

are sometimes of importance, especially when a difference of at least 1 C (33.4 F) is shown in symmetrical areas. The chief value of determinations of surface temperature, however, consists in following their response to certain procedures that normally affect the vasomotor activity in the extremity. Thus, if vasoconstriction is well marked, as it normally is or can be induced, in the distal part of the lower extremity, the surface temperature should show a striking increase when the sympathetic vasoconstrictor fibers are paralyzed.

We determined the surface temperatures in a group of persons with apparently normal vascular systems before and after the induction of spinal anesthesia for various types of operations (fig 2). With the exception of a small group, which we shall presently discuss, all of these

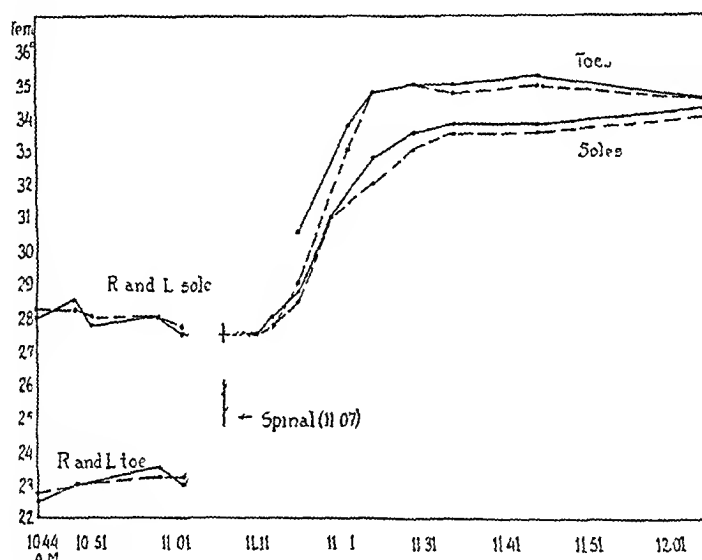


Fig 2 (case 32599) —Normal response to spinal anesthesia in a case in which hermotomy was performed on the right side (normal blood vessels). Temperatures of toes and soles rise sharply and come to the same level.

patients showed a sharp increase in the surface temperatures of the feet on the establishment of complete anesthesia in that area. After a few observations, it was evident that this furnished a satisfactory basis for demonstrating the presence of vasoconstriction. We later learned that simultaneously in at least two other clinics this same procedure was being developed as a qualitative test for vasoconstriction.⁶ After assembling a group of twenty-two such curves in normal persons, a careful study of them yielded further important information. The curves showing a sharp rise in surface temperatures regularly reached

6 White, J. C. Diagnostic Blocking of Sympathetic Nerves to Extremities with Procaine, *J. A. M. A.* **94** 1381 (May 3) 1930. Brill, S., and Lawrence, L. B. Changes in Temperature of the Lower Extremities Following the Induction of Spinal Anesthesia. *Proc. Soc. Exper. Biol. & Med.* **27** 728, 1930.

a level at which they remained for a considerable time, then gradually declined to approximately the original point (fig 3). Furthermore, the level that the colder part of the extremity (usually the toes) attained was approximately the same on both sides and also the same as that reached by other parts of the extremity. On comparing this temperature with the original temperature of the warmest part of the exposed body, it was again found to be approximately the same. On studying these results mathematically, we were surprised to find in these twenty-two cases that the height of the temperature attained by the surface of the great toe always fell within 1.5 degrees of the mean. In other words, even without correction for room temperature, which varied considerably in the first series, the skin in these normal extremities became approximately uniformly warmer, not only throughout the extremity,

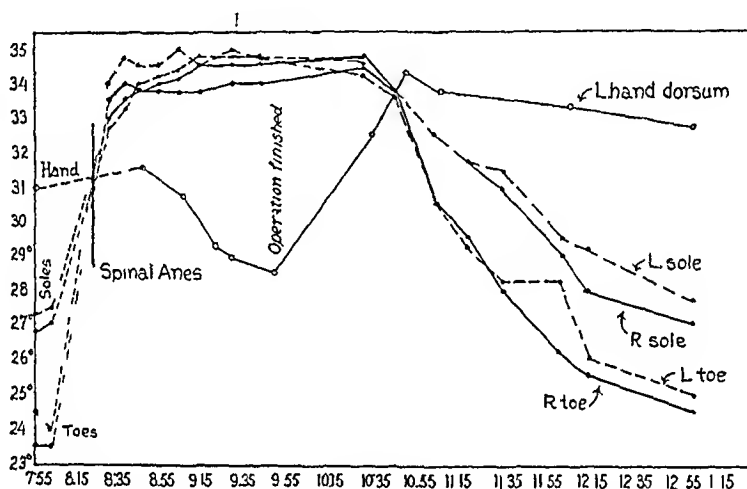


Fig 3 (W S 34172) —A normal vasodilatation level, reached by the toes and soles following spinal anesthesia in a case in which herniotomy was performed, is maintained as long as the complete anesthesia lasts (about two hours). As sensation and motion return to the extremities, the temperatures of the toes and of the soles fall approximately to the point from which they started (reappearance of vasoconstrictor gradient). The hand, not being anesthetized, shows a fall in surface temperature during the operation (psychic and mechanical influences). The room temperature was 24.9 C.

but on comparison of one person with another. We named the level attained the normal vasodilatation level,⁷ as it seemed to represent the circulation entirely freed from vasoconstrictor impulses. Three cases were found that did not respond by a sharp rise in surface temperatures after satisfactory spinal anesthesia. In these patients (fig 4), though the peripheral circulation did not appear grossly abnormal, the skin temperature of the toes and soles started at a very high level, in fact,

⁷ Morton, J. J., and Scott, W. J. M. The Measurement of Sympathetic Vasoconstrictor Activity in the Lower Extremities, *J. Clin. Investigation* 9:235, 1930.

nearly at the vasodilatation level, and either remained about the same or fell after spinal anesthesia. All three of these patients were markedly cachectic and had advanced carcinoma. Apparently, their condition had already produced a liberation of the peripheral vessels from vasoconstriction. We shall later refer to this same phenomenon in certain vascular diseases. These three cases of carcinoma are examples of Ipsen's narcosis sign,⁸ namely, an unfavorable prognosis in persons with presumably normal peripheral blood vessels when the skin temperature in the foot does not rise under general anesthesia. We felt that further information in regard to vasoconstrictor activity could be obtained by studying the effect of other forms of anesthesia. Surgeons have long known that there is a peripheral vasodilatation under general anesthesia. This phenomenon was extensively studied by Ipsen,⁹ who used a simple scheme which shows the major changes. We wanted to get further evidence, however, in regard to the level and the mechanism of this

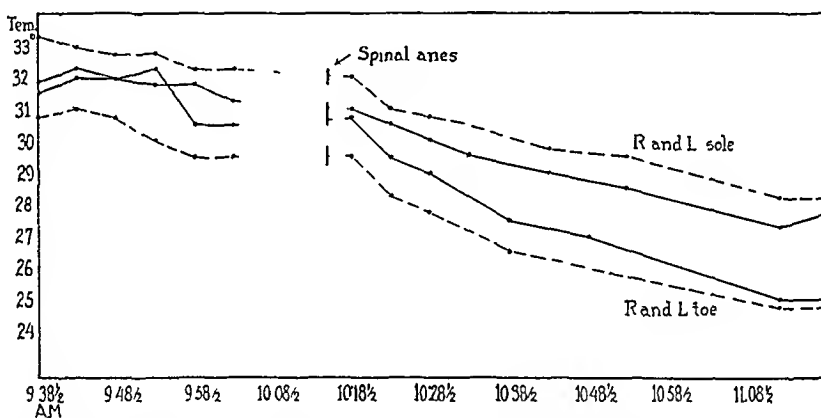


Fig 4 (case 32374) —Unusual response of normal vessels to spinal anesthesia in a few cachectic persons, as shown in a case of carcinoma of the gallbladder (normal blood vessels). The temperature does not rise after spinal anesthesia, but starts at a high level.

dilatation. Does general anesthesia produce the same complete relaxation of vasoconstriction as that seen following spinal anesthesia? We soon found that nitrogen monoxide-oxygen, ether, and tribromethanol, either alone or in sequence, produced the same characteristic sharp increase in the surface temperatures of the feet that was observed under spinal anesthesia¹⁰ (fig 5). Also after from twenty minutes to

8 Foged, J. Ipsen's Narkosephanomen, *Deutsche Ztschr f Chir* **229** 365, 1930.

9 Ipsen, J. Les arteres et l'anesthésie, *Acta chir Scandinav* **6** 487, 1929.

10 A preliminary report of the effect of general anesthesia on vasoconstriction was given before the Society for Experimental Biology and Medicine. Scott, W. J. M., and Morton, J. J. Obliteration of Vasoconstrictor Gradient in the Extremities under Nitrous Oxide-Oxygen, Ether, and Tribromethyl Alcohol Anesthetics. *Proc Soc Exper Biol & Med* **27** 945, 1930.

half an hour the elevation of the skin temperature reached and held the normal vasodilatation level. Figure 6 shows how the surface temperatures of the hand, the sole and the plantar surface of the great toe all

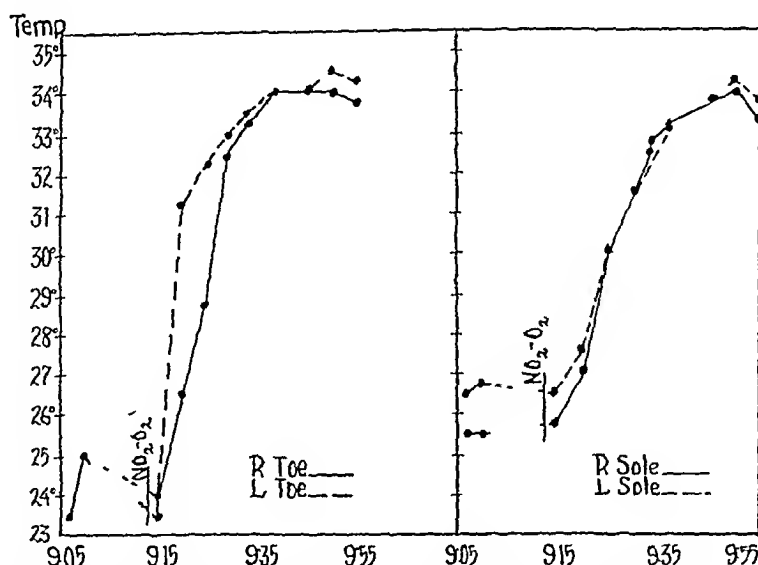


Fig 5—Obliteration of normal vasoconstriction by nitrogen monoxide-oxygen in a case in which herniotomy was performed on the right side

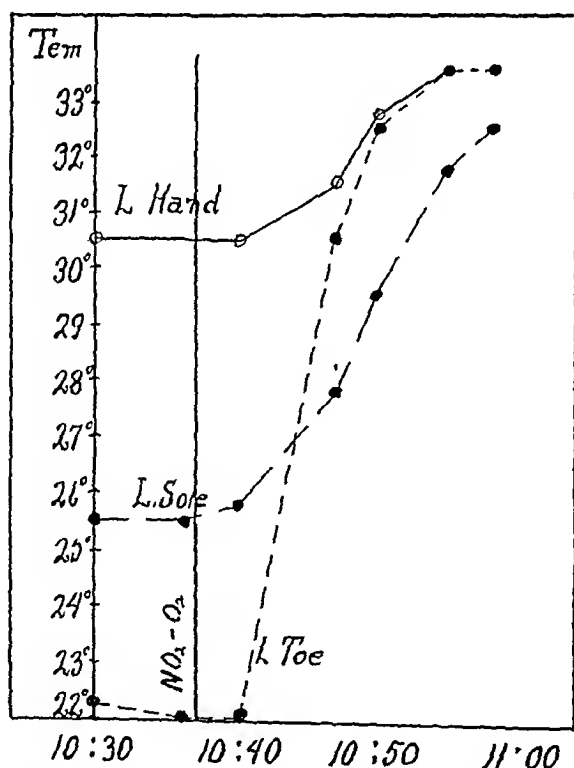


Fig 6 (case 35082)—Normal vessels. All parts of the extremities come to the normal vasodilatation level (obliteration of the vasoconstrictor gradient)

come to within 1 degree of each other, the vasomotor gradient of the extremity has been obliterated. Furthermore, after this level has been attained either by spinal anesthesia or by one inhalation agent, the addi-

tion of another anesthetic does not alter the surface temperature (figs 7 and 8) Here there is additional evidence that when once the vasodilatation level is reached, the vessels are devoid of vasoconstrictor influence There are a few sources of error to avoid in testing for

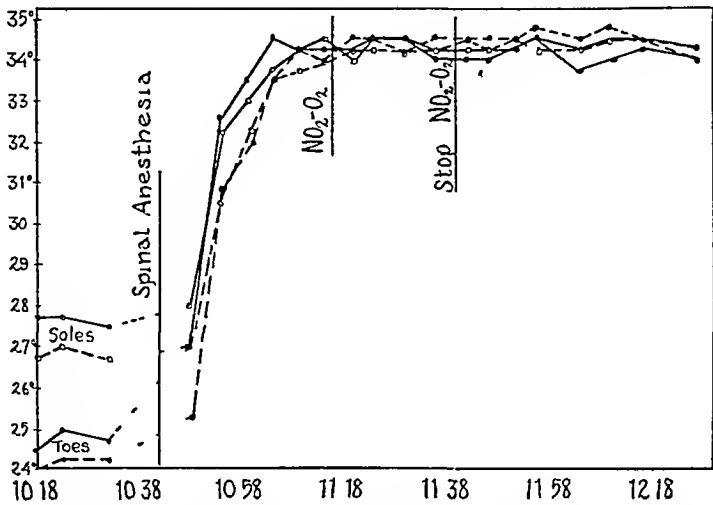


Fig 7—When the normal vasodilatation level is obtained by spinal anesthesia, the addition of an inhalation anesthetic produces no further effect, as shown in a case in which exploratory laparotomy and ventral herniotomy were performed

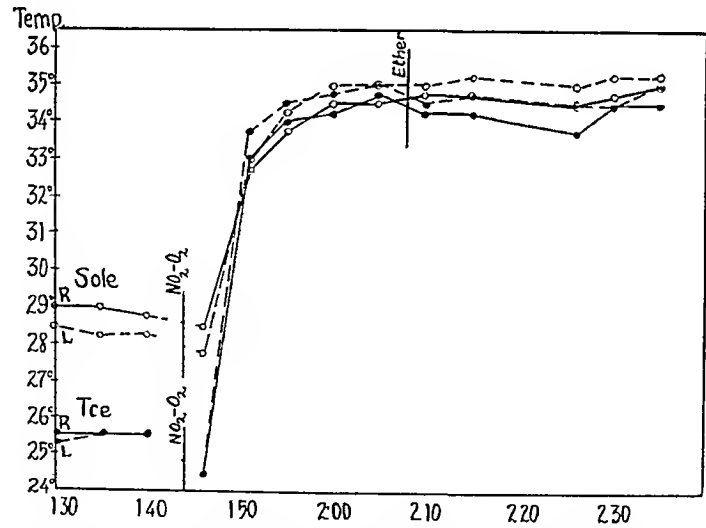


Fig 8—When the normal vasodilatation level is obtained by one inhalation anesthetic, the addition of another produces no further effect, as demonstrated in a case in which exploration of the wrist was done

this normal vasodilatation level In the first place, the anesthesia in the affected area must be complete if the nerve fibers are blocked chemically (as in spinal anesthesia) In the second place, under general anesthesia a sufficient depth must be attained to provide muscular relaxation (figs 9 and 10) In the third place, occasionally some local abnormality

of the skin, such as a scar or an extensive callus, will interfere with the normal vascular response at that point. In fact, where the skin is especially thick, the curve of temperature changes is a little slow in rising to its maximum point. Thus, often the temperature of the toe

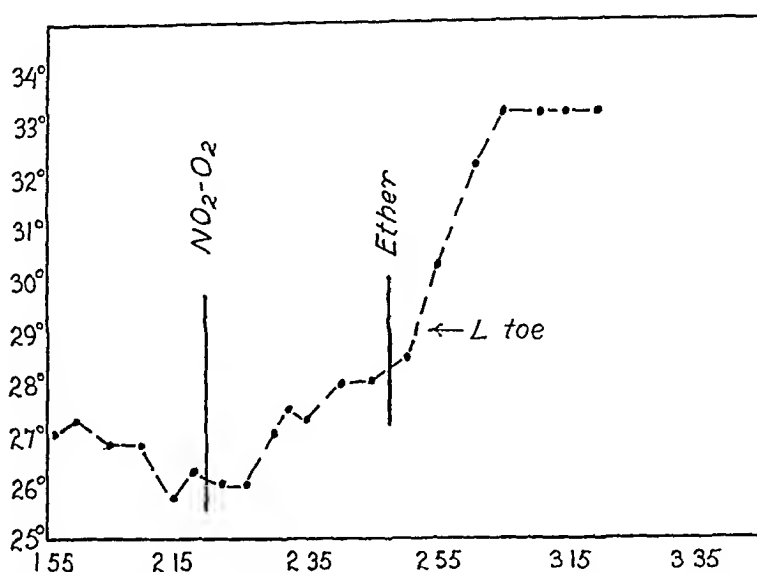


Fig 9 (S B 24432) —Depth of general anesthesia necessary to provide muscular relaxation. Relaxation was not obtained in this case by nitrogen monoxide-oxygen alone. Note the unsatisfactory effect on vasoconstriction. On the addition of ether, with relaxation, note the prompt response of the skin temperatures to the normal vasodilatation level. The room temperature was 25.4 C.

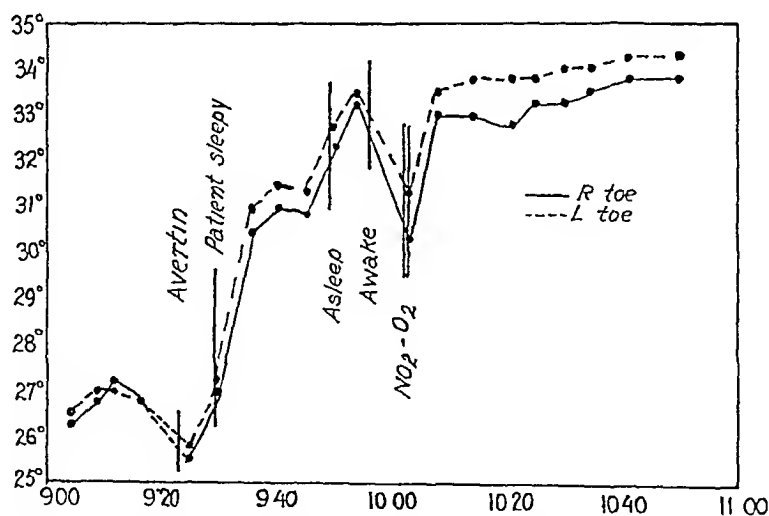


Fig 10 (C B 33971) —Normal vessels, release of vasoconstriction by anesthesia with tribromethanol (in amylene hydrate solution) in a case in which laparotomy was performed for exploration. When the patient was moved to the operating table he awakened, with the recurrence of some vasoconstriction. Nitrogen monoxide-oxygen was then administered, with a prompt return to the vasodilatation level. The room temperature was 25.4 C.

reaches the vasodilatation level more promptly than that of the sole. When the present work was started, the surface temperature was deter-

mined by a mercury thermometer so constructed that the sensitive surface was flat and could be applied to the skin. The bulb of the thermometer was covered with cotton or felt. This method is similar to the procedure that Ipsen used. This was sufficient to give the major swing of the temperature, but did not accurately measure the surface temperature, owing to the retention of heat underneath the felt. The same objection applied also to the usual thermocouple, which took from thirty to forty-five seconds to come to equilibrium. Consequently, a simplified and more sensitive apparatus was perfected, which required about five seconds for each reading¹¹. This interval furnishes a true skin temperature determination without the distortion of heat storage under the apparatus.

By avoiding the errors mentioned, we then had two methods either one of which was entirely satisfactory for obliteration of vasoconstrictor activity, namely, spinal anesthesia and general anesthesia. These left nothing to be desired in studying such reactions in any one requiring one of the types of anesthesia for an operation. By this time, however, we had found the test indispensable in the study of any vascular lesion in the extremity. We therefore wished to simplify the procedure so that it could be applied with a minimum of discomfort to ambulatory patients and could be repeated at intervals without inconvenience. It is well established that the sympathetic motor fibers to the vessels of the extremity are segmentally distributed. Weir Mitchell¹² carried out the experiment of temporarily interrupting impulses through a mixed nerve by freezing his own ulnar nerve, and found an immediate increase in temperature in the anesthetized skin field. He also credited Waller with a similar result. Braun,¹³ in 1903, emphasized the vasomotor paralysis with hyperemia and hyperthermia limited to the anesthetized area that follows conduction anesthesia. Wiedhopf¹⁴ made an extensive study of this hyperthermia associated with nerve blocking, and advised its use in determining the necessary height for amputation. In fact, he presented evidence suggesting that the vasomotor fibers were more sensitive to the paralyzing action of procaine hydrochloride than the sensory or

11 This apparatus was developed under our direction by the Taylor Instrument Company of Rochester, N. Y. Scott, W. J. M. An Improved Electrothermal Instrument for Measuring Surface Temperatures, *J. A. M. A.* **94** 1987 (June 21) 1930.

12 Mitchell, S. Weir. Cases of Lesions of Peripheral Nerve Trunks with Commentaries, *Am. J. M. Sc.* **86** 17, 1883.

13 Braun, H. Experimentelle Untersuchungen und Erfahrungen über Leitungsaesthesie. *Arch. f. klin. Chir.* **71** 179, 1903.

14 Wiedhopf, Oskar. Experimentelle Untersuchungen über die Wirkung der periarteriellen Sympathectomie und der Nervenvereinigungen auf die Gefässe der Extremitäten. *Beitr. z. klin. Chir.* **130** 399, 1924.

motor fibers. He also advised freezing the nerve trunks in arteriosclerotic gangrene, not only for the relief from pain, but for the dilatation of the arteries, showing that he had not learned to distinguish the spastic and occlusive elements of vascular disease by this method. Lewis and Landis¹⁵ and White⁶ suggested the application of this method in the qualitative demonstration of arterial spasm. We first investigated the response of normal persons to such conduction block. Our purpose was to determine how the degree of vasodilatation under such conditions would compare with the normal vasodilatation level previously established. It is obvious that even if all of the vasoconstrictor impulses in the peripheral field are interrupted, on anesthetization of a nerve trunk, vasoconstriction will be present in the larger vessels of

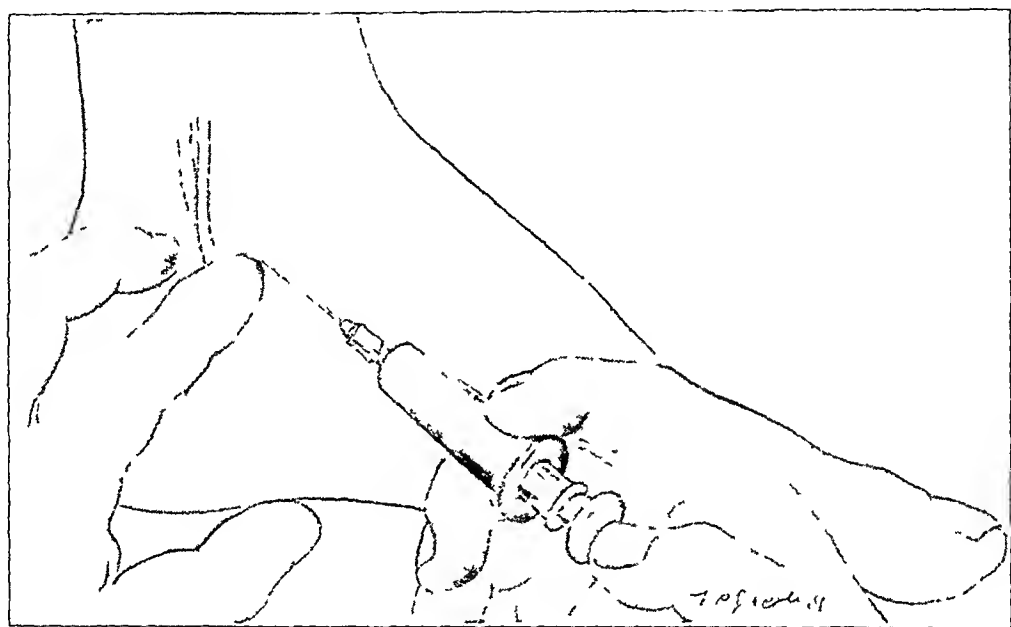


Fig. 11—Landmarks for posterior tibial nerve block. The nerve is located by palpation and is immobilized with the finger as far distally as it can readily be felt. Injection at this point is distal to the point at which the nerve passes under the posterior tibial artery.

the leg. What proportion of the increase in peripheral circulation seen after spinal and general anesthesia will be obtained under peripheral nerve block? This point required elucidation before the method could be used quantitatively to determine spasm and occlusion in pathologic cases.

In the majority of instances, the problem of peripheral vascular diseases is chiefly concerned with the feet. Consequently, we wished to produce complete anesthesia in a skin area in the most distal part of the

15 Lewis, T., and Landis, E. M. Some Physiologic Effects of Sympathetic Ganglionectomy in the Human Being and Its Effect in a Case of Raynaud's Malady, *Heart* 15:151, 1930.

toot This was easily obtained by infiltration about the posterior tibial nerve a little below the internal malleolus (fig 11) The nerve at this point can almost always be felt after it has passed under the posterior tibial artery If procaine hydrochloride is infiltrated into this region, conduction block anesthesia of the corresponding skin field involves most of the sole and the plantar surfaces of the heel and of all of the toes This procedure was carried out in sixteen persons (medical students) with normal blood vessels, and it was found that the same form of curve was obtained in the anesthetized area that ensued after spinal or

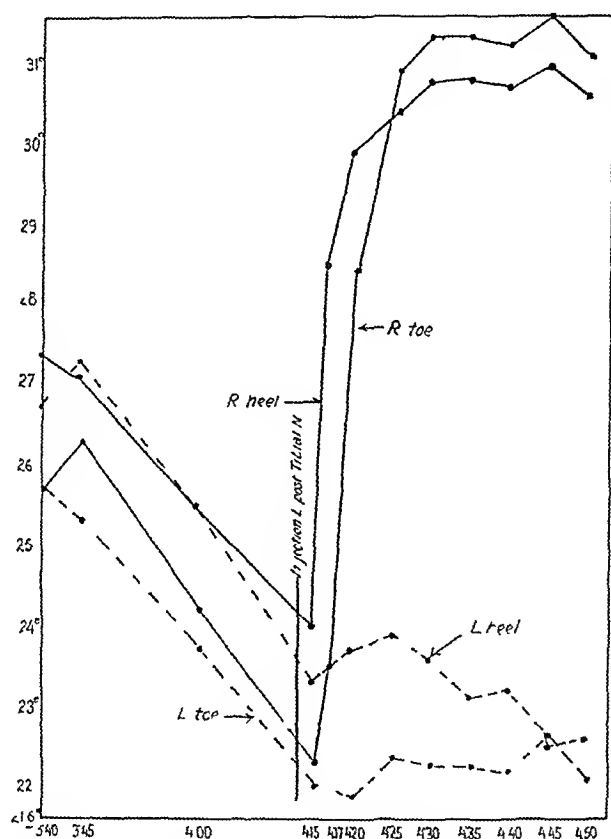


Fig 12—Normal vessels showing vasodilatation obtained following conduction block of the left posterior tibial nerve in R W The temperature of the room was 20 C

general anesthesia (fig 12) Under standard conditions, the height of the curve in these normal persons came within a range of 15 degrees, but the mean of the maximum temperatures obtained under conduction block was about 1 degree below that obtained under spinal or general anesthesia Consequently, it seemed clear that in the involved area all but a small fraction of the increased circulation that follows spinal and general anesthesia was obtained by blocking the vasoconstrictor fibers in the nerve trunk only a few inches from the peripheral field In order to verify this, the maximum surface temperature readings of

the foot of the same person were compared following conduction block of the posterior tibial nerve with those obtained shortly thereafter under general anesthesia (fig 13). The skin temperature of the great toe reached its height at 32.9 C (91.2 F) under the nerve block, while its maximum under nitrogen monoxide-oxygen and ether anesthesia was 33.6 C (92.5 F). It is apparent, then, that conduction block is a satisfactory method of estimating vasoconstriction, though in borderline pathologic cases it is probably desirable to check the data so obtained with the result of either spinal or general anesthesia.

We have shown the effect on the surface temperatures of the extremities of the temporary abolishment of vasoconstriction by three

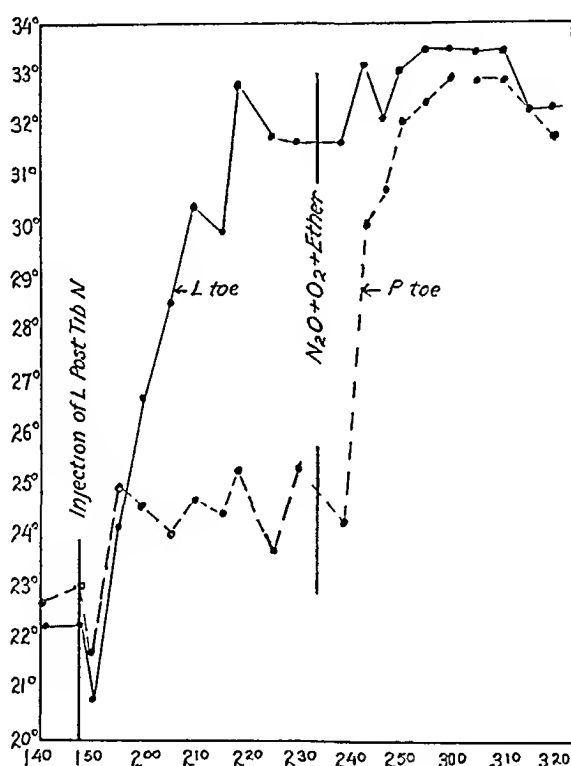


Fig 13—Normal vessels, comparison of vasodilatation obtained by blocking the left posterior tibial nerve with that following inhalation anesthesia in J J. The temperature of the room was 22 C.

different methods, and have established the normal vasodilatation level by these procedures as follows: at a room temperature of 20 C (68 F), the surface temperature of the great toe reaches at least 31.5 C (88.7 F) with general or spinal anesthesia and 30.5 C (86.9 F) with nerve block of the posterior tibial nerve. (If the determination is carried out in a warmer room, a correction factor of 0.3 C [32.5 F] should be added to these levels for each degree centigrade by which the room temperature exceeds 20 C.) By comparing the effect obtained in pathologic cases with these figures for the normal response, we are

now able to divide all peripheral vascular disturbances in the extremities into three main categories. The circulatory symptoms in the respective groups are due to (1) occlusion alone, (2) spasm alone and (3) mixed spasm and occlusion. Most cases of endarteritis obliterans, whether of diabetic or of arteriosclerotic origin, fall into the first group of occlusion alone (figs 14 to 17). Probably most cases of Raynaud's disease and many of the cases that have been classified as thrombo-angitis obliterans respond in their earlier stages to anesthetization of the vasoconstrictor fibers with a dilatation to the normal level (figs 18 to 20). Many examples of thrombo-angitis obliterans and also some of syphilitic arteritis show both spasm and occlusion by this test (figs 21 and 22).

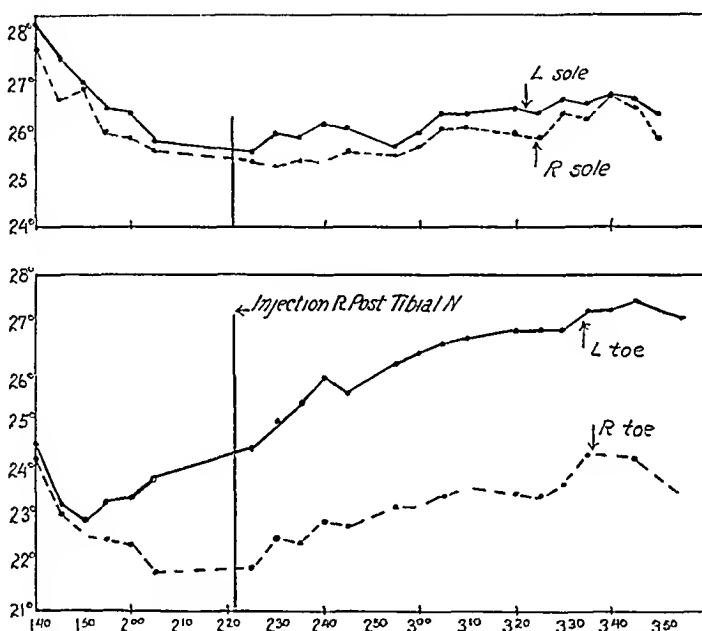


Fig 14—Endarteritis obliterans in C W. No palpable pulses in either foot. Right toes show marked dependent rubor. Gangrene threatened on the right, not on the left. Injection of the right posterior tibial nerve causes no significant increase in temperatures. Gradual increase in surface temperature of left toe occurs on the unanesthetized side. Interpretation: circulatory deficiency in right foot due to occlusion without spasm. Room temperature was 20 C.

In the first group (occlusion), with the establishment of a satisfactory anesthesia by any of the three methods outlined, there is practically no increase in the surface temperature of the involved part. Frequently, the most distal part of the extremity will show this type of response, while a small amount of vasoconstriction can still be demonstrated in more proximal areas. The second group (spasm) includes many examples in which the history strongly suggests a spastic lesion by the extreme variation of symptoms during different periods. This is, of course, particularly well exemplified by the white and blue phases of

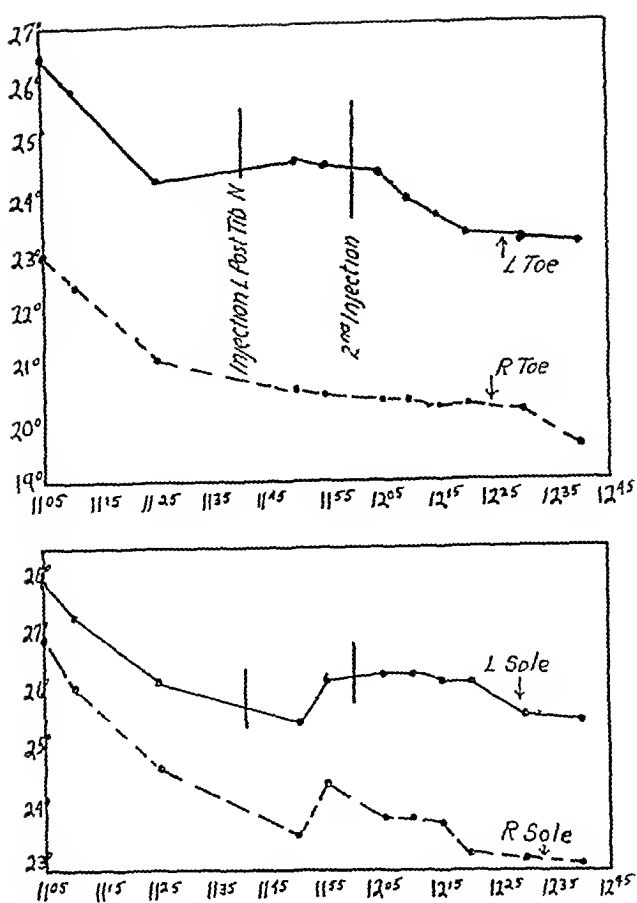


Fig 15—Endarteritis obliterans in a man, aged 41. Circulation in the left foot dangerously impaired, with a small indolent ulcer on the dorsal surface of the left great toe. Conduction block of left posterior tibial nerve was not followed by increase in temperature, indicating occlusion without spasm. Temperature of the room was 21.1 C.

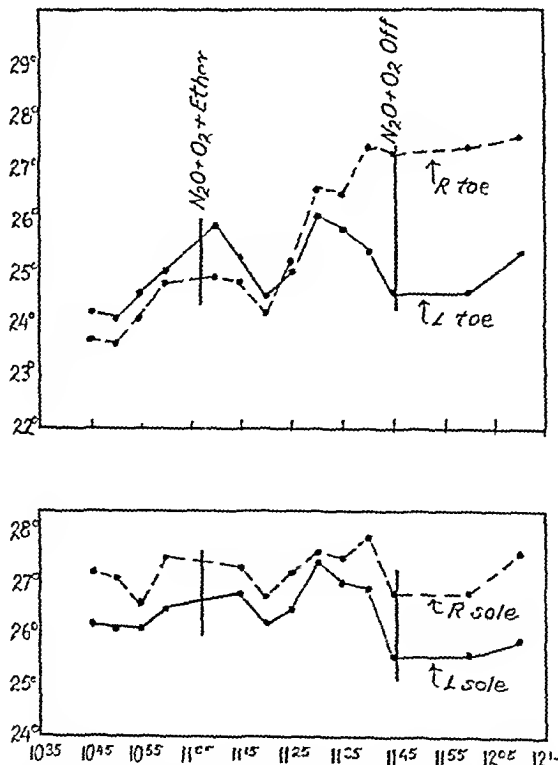


Fig 16—Diabetic endarteritis obliterans in Mr E S. No increase in surface temperature of the left toes, those on the right show very slight increase with an occlusion index of 5 C. The temperature of the room was 21.1 C.

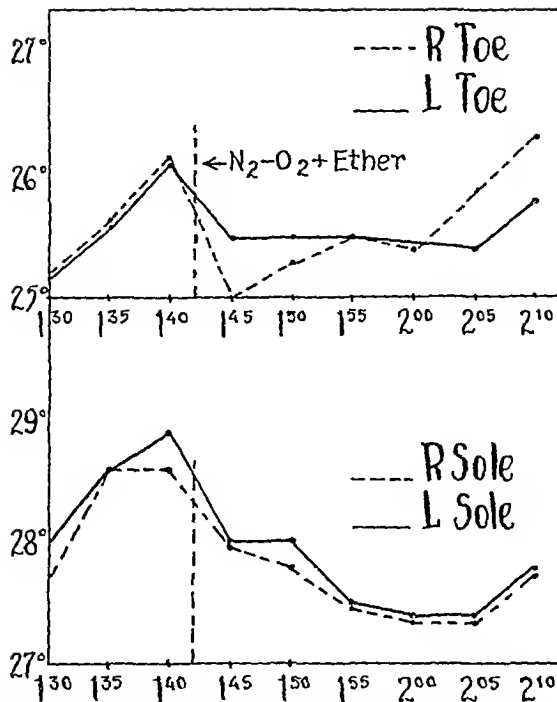


Fig 17 (case 6756) —Diabetic endarteritis obliterans No increase in surface temperature after inhalation anesthesia Occlusion without spasm Temperature of the room was 21.1 C

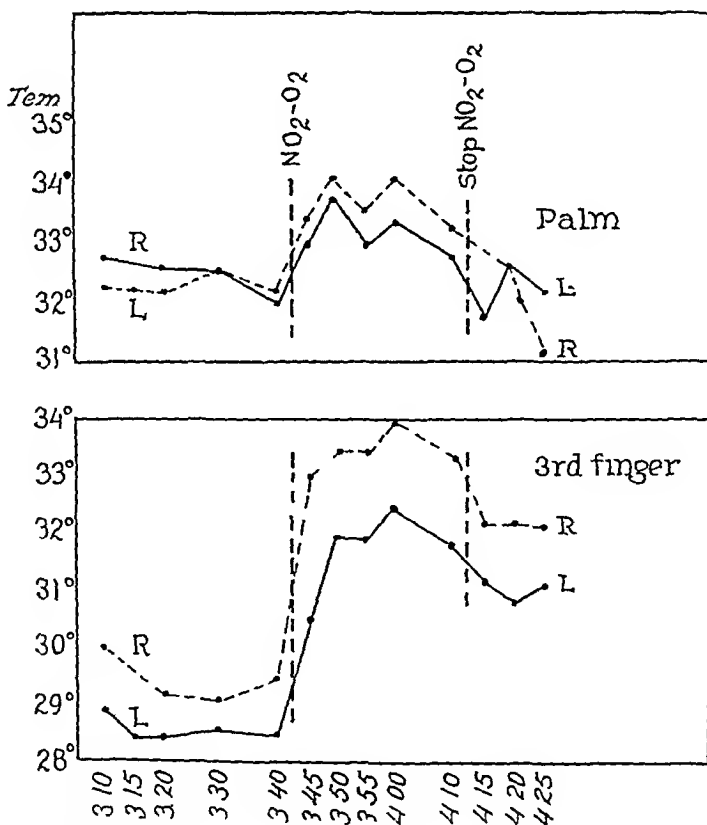


Fig 18—Angiospasm of the hands (Raynaud's type) Following inhalation anesthesia, the right third finger reaches the vasodilatation level The left shows a marked increase, but remains nearly 2 degrees below the right, showing a slight occlusion index in the left third finger. This corresponds with the clinical picture, as there had been a superficial area of necrosis on the left third finger, leaving a scar

Raynaud's disease, with intervening periods of normal color and apparently normal circulation. But many times it is found that spasm is the outstanding cause of symptoms in cases of common vascular diseases that appear clinically exactly like the outspoken members of the occlusion group. A large number of the present vascular diseases show both spasm and occlusion. Obviously, there are many degrees in the exact proportion of each of these two elements in the various cases. Some show a mere trace of spasm still present, while others attain almost the normal levels after anesthesia. To designate the proportions of spasm

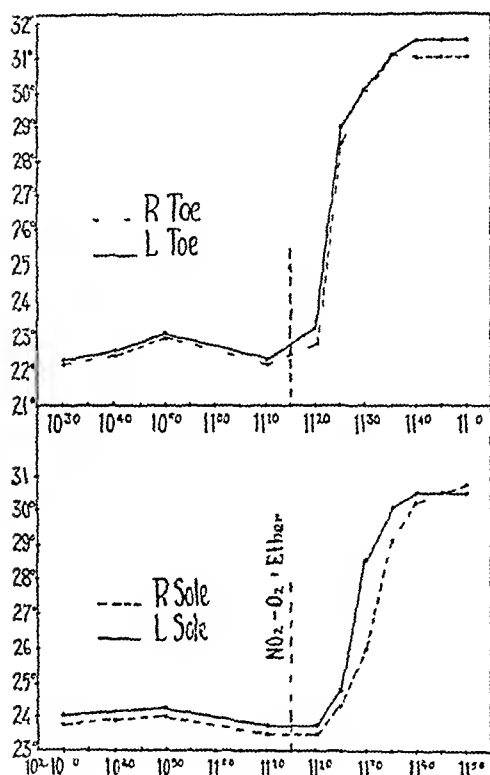


Figure 19

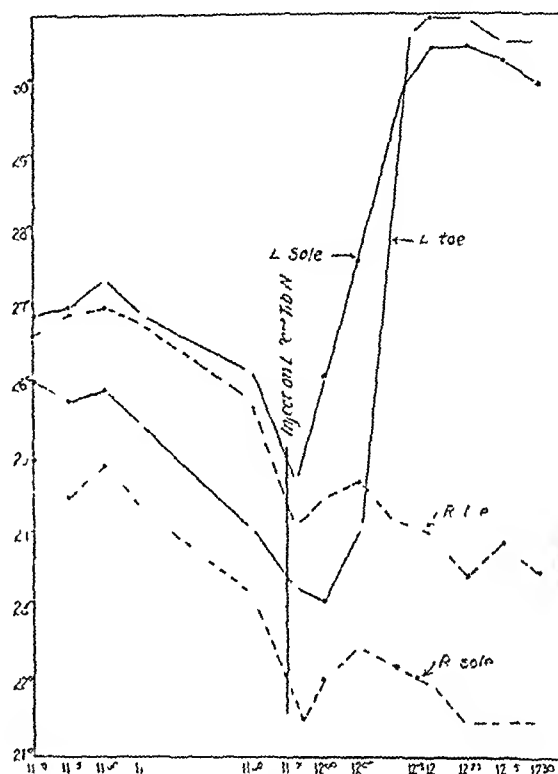


Figure 20

Fig 19 (case 42685)—"Diabetic endarteritis obliterans," clinical diagnosis. Circulatory impairment causes pain and disability, more severe on the right. Test with inhalation anesthetic shows circulatory symptoms chiefly due to spasm. Occlusion index about 1 C. The room temperature was 22.7 C.

Fig 20—Same effect shown by conduction block of left posterior tibial nerve in a case of arteriospasm in F. C. S. Compare the heights of the temperatures obtained under nerve block and inhalation anesthetics. Temperature of the room was 20 C.

and occlusion in any area, the highest surface temperature (centigrade) attained is subtracted from the lowest normal reading established for the type of anesthesia used. This figure is called the occlusion index and is of importance in determining the type of treatment to be adopted in the mixed group. We may emphasize here the fact that

these clinical groups are established on the basis of their physiologic response rather than on a pathologico-anatomic basis. Probably a certain amount of organic occlusion caused by thrombosis or by narrowing of the lumen is present in nearly all of the cases of vascular disease,

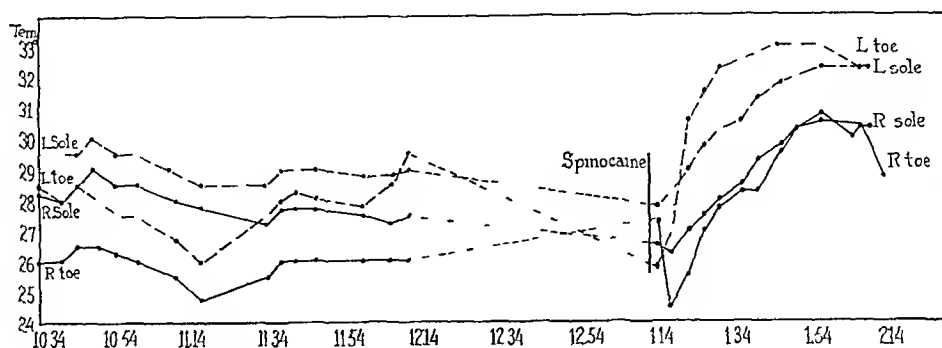


Fig 21 (case 31391) —Syphilitic endarteritis obliterans. No pulsations in the right foot and feeble pulsations in the left. Circulation seriously impaired on the right. Following spinal anesthesia left foot comes up to the normal vasodilatation level. Right foot shows a definite but incomplete rise with an occlusion index of 2.5 C.

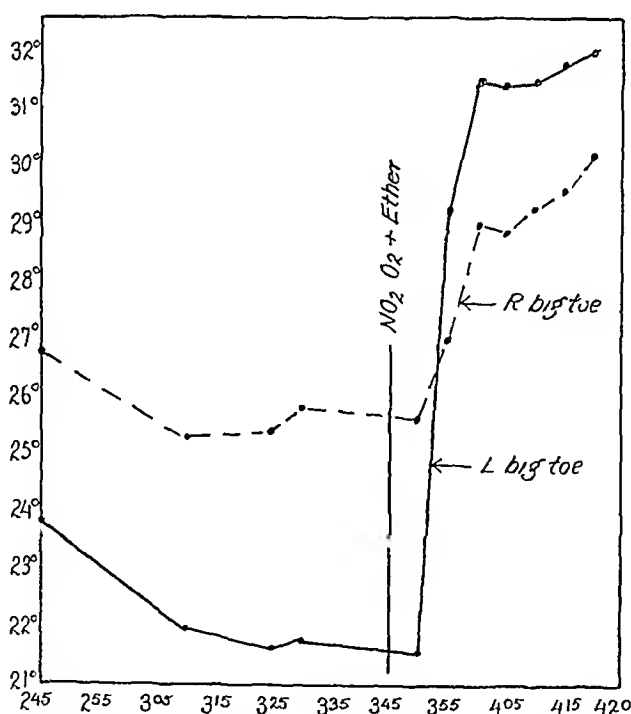


Fig 22 —Thrombo-angitis obliterans with migratory phlebitis in P. B. Symptoms at present limited to the right. Inhalation anesthesia shows response on the left to the normal vasodilatation level, on the right, a definite but incomplete rise. Occlusion index, 2 C. Temperature of the room was 21 C.

with the exception of the earlier stages of Raynaud's disease. But there is an important difference in the effect of such changes on the

circulation of the foot, primarily owing to the behavior of the collateral and terminal vessels. The location of these important arteries is visualized in the accompanying roentgenograms. Figure 23 shows an intra vitam injection of the arterial tree with an iodine salt. An obstruction in the posterior tibial artery is seen, the small anastomotic branches running parallel to the main vessel can be followed down to

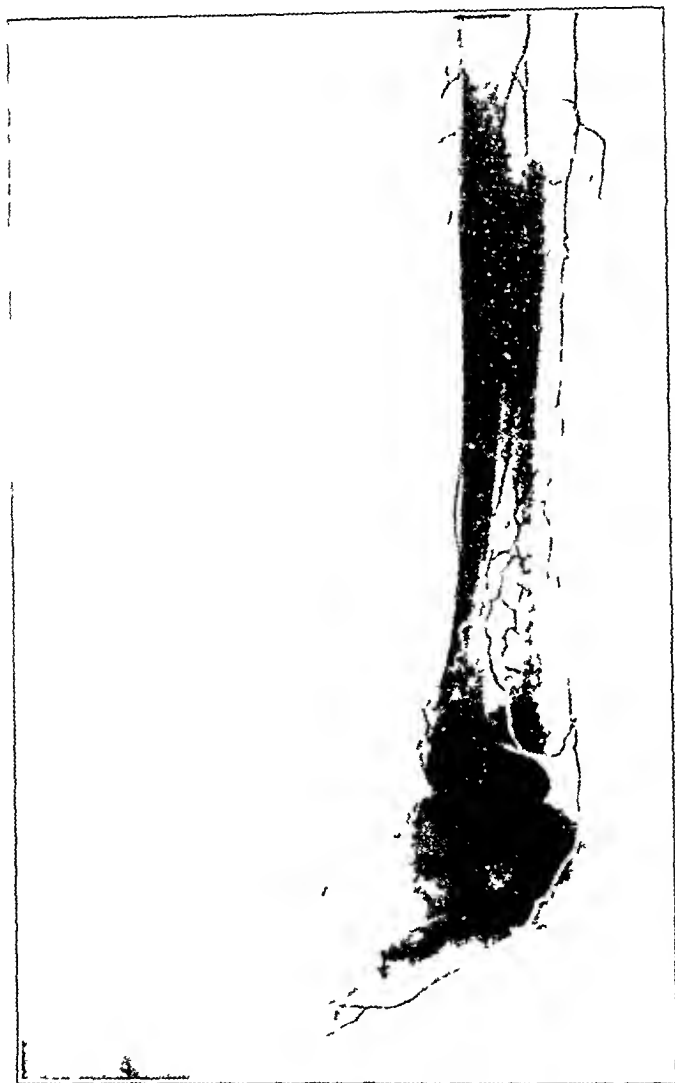


Fig 23—Arteriosclerosis with occlusion of posterior tibial artery, intra vitam injection. This figure is shown to illustrate the collateral circulation through the small vessels. The posterior tibial artery blocked in about the middle of the calf is reconstituted opposite the malleolus (retouched photograph)

the point where the channel is reconstituted in the main artery about opposite the internal malleolus. Figure 24 shows an injected specimen of a leg amputated on account of infection. It shows very nicely the smaller terminal arteries in the foot. In advanced noninflammatory occlusive disease, such as that typically seen in arteriosclerosis or diabetic endarteritis, vasoconstriction, even that amount usually present in nor-

mal persons, is lacking. Apparently some compensatory mechanism has released the anastomotic and terminal arteries and arterioles from all vasoconstrictor effects (figs 25 and 26). It is exactly thus that vascular disease associated with spasm differs from the occlusive form. In advanced stages of arteriospasm threatening the viability of the part,

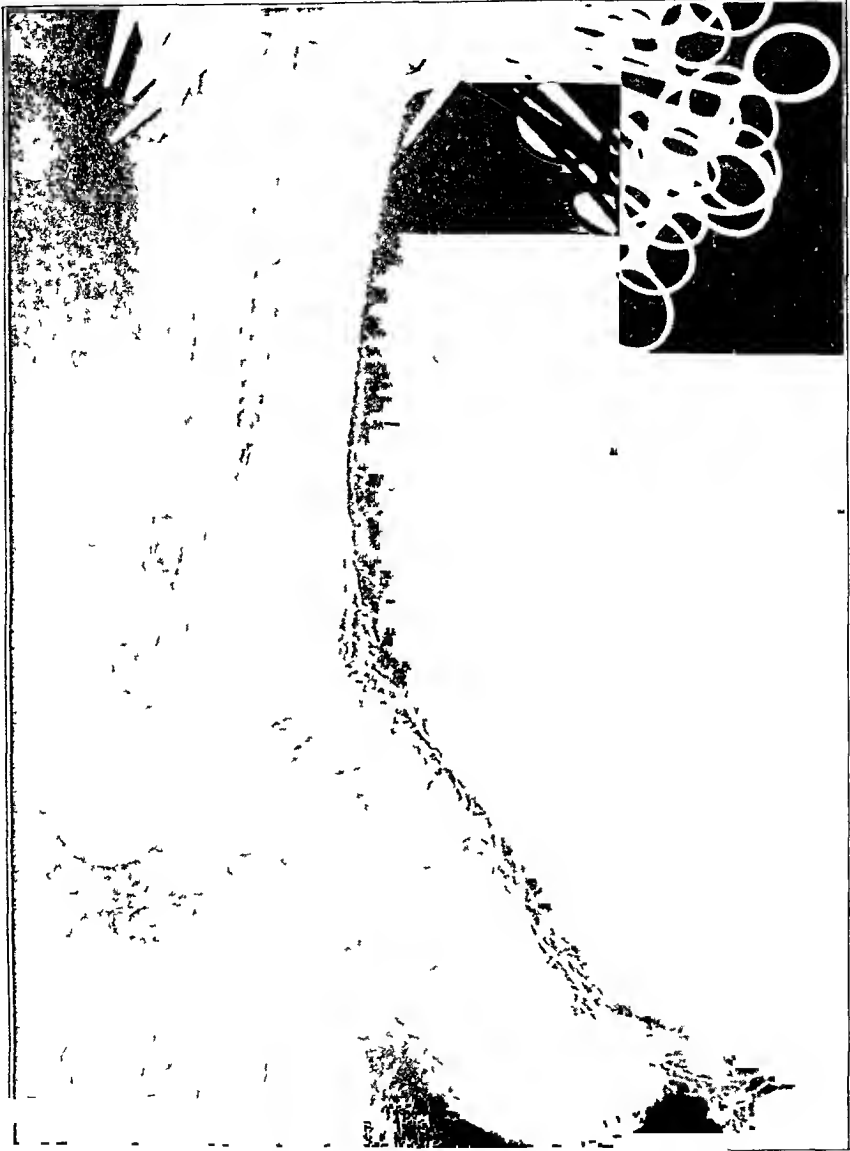


Fig 24—Injection of amputated extremity to illustrate the terminal finer arteries. Note the occlusion of the posterior tibial artery in the lower third of the leg shown between the tibia and fibula. The viability of the foot is more dependent on the anastomotic and terminal arteries and arterioles than on the main arteries in the lower leg.

vasoconstriction still persists and is not released by the compensatory mechanism seen in the occlusive group. What causes this difference? We do not yet have final proof, but it is our hypothesis that the inflam-

matory reaction extending through the wall of the vessels, which is so characteristic pathologically of thrombo-angitis obliterans, affects the afferent nerve fibers in the adventitial coat or even in the accompanying nerves themselves. This sets up a reflex vasoconstrictor spasm, the particular importance of which is that it involves not only the diseased main arteries, but the collateral and terminal small vessels in the periphery. Consequently, when the circulatory deficit reaches a certain

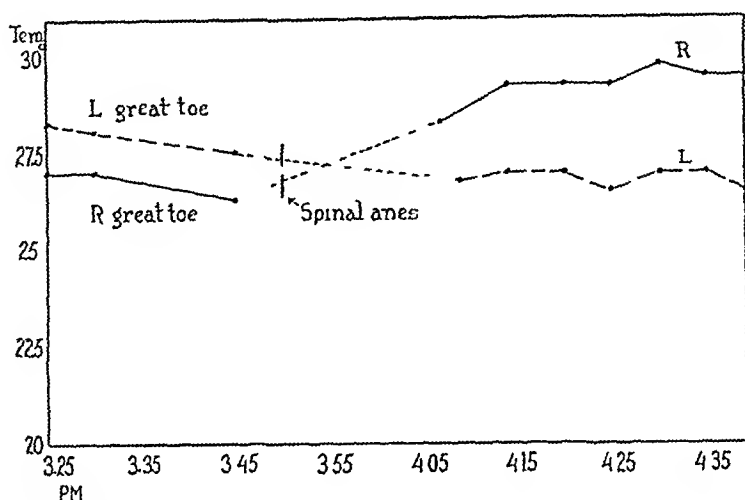


Fig 25 (case 31766) —Endarteritis obliterans on the left. No pulsation on the left, feeble on the right. Circulation of left foot dangerously impaired. Left great toe shows no rise after spinal anesthesia, right great toe shows slight increase. Note that the side with the more seriously involved peripheral circulation starts at a higher level and shows no vasoconstriction, while the less involved side shows a slight amount of vasoconstriction still present.

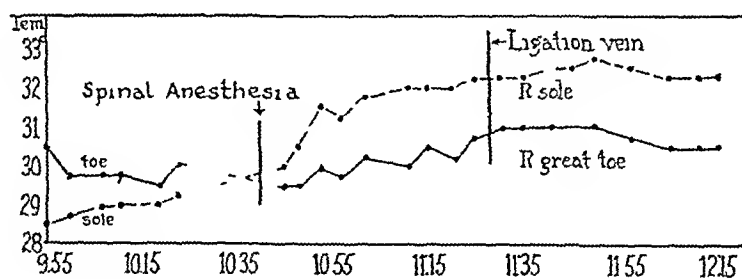


Fig 26 (case 26956) —Diabetic endarteritis obliterans (arteriosclerotic vessels). Left leg amputated previously. Circulation in right toes seriously impaired. Following spinal anesthesia, no increase in surface temperature of the toes, but definite increase in the sole. Note particularly the reversal of the normal vasoconstrictor gradient, with the temperature of the toe starting at a higher initial level than that of the sole, owing to the absence of vasoconstriction in the toe.

point in occlusion it brings into play the compensatory release of normal vasoconstriction, but in the spastic group this reflex vasoconstriction continues. We have found that in vascular disease the efficiency of the circulation to the distal part of the extremity is much more dependent

on these smaller arteries than it is on the main arterial trunk. An illustration of this is found in a case of arteriosclerotic endarteritis in which there was diminution or absence of pulsation in all four major vessels of both feet. However, the left dorsalis pedis artery could barely be felt, the right was not palpable. This greater impairment of the large vessels in the lower part of the right leg was borne out by the following oscillometric readings. On the left side, the swing was one and one-half major divisions, while on the right side it was only one-half. Yet in spite of the more complete occlusion of the larger arteries, the temperatures of the right toes were 1 degree higher than those of the left, showing a more rapid peripheral circulation on the side with the more defective major arteries. This phenomenon was probably due to the fact that the left side was still affected by vasoconstriction, while on the right side the compensatory mechanism had released it.

A review of the relationship of sympathetic stimuli to peripheral blood vessels shows a varying degree of vasoconstrictor activity in the normal person. In occlusive disease without inflammatory reaction in the outer wall of the blood vessels, this normal vasoconstriction is released when the circulation becomes seriously impaired. In spastic disease, vasoconstriction continues even when the reduced circulation to the part endangers its viability. When some of the anastomotic and terminal vessels become occluded also, the mixed type results. There are many more examples of spasm among the common diseases of the peripheral blood vessels than is usually realized.

TREATMENT

The differentiation of occlusive and spastic vascular disease and the estimation of the relative proportions of each when both are present are of prime importance, because the principles on which the treatment for these groups must rest differ radically (fig 27). In the group in which symptoms are entirely dependent on occlusion, nothing whatever is gained by the elimination of vasoconstrictor activity. Sympathectomy for such patients is unjustifiable. Besides symptomatic relief from discomfort and the avoidance of infection, treatment should be directed to one end, namely, a more efficient peripheral distribution of the blood. Venous ligation seems to offer some assistance in this direction. It is probably in this manner also that pain in such cases may be somewhat alleviated by depression of the level of the feet, gravity thereby being used to assist in the forcing of blood through the most distal parts. It is not our purpose to discuss extensively the treatment for occlusion. We want particularly to emphasize that there is no evidence of participation of the sympathetic activity in this group. On the other hand, in conditions in which spasm is present the treatment is entirely different.

and should consist in measures to overcome the spasm. There are several ways in which this problem may be attacked.

1 *Overcoming the Inflammatory Process*.—The most direct and satisfactory procedure would be to overcome the inflammatory process. In syphilitic vascular disease this can sometimes be achieved, and the possibility of this specific agency being the cause of the condition should always be considered, particularly in the mixed group showing both spasm and occlusion. It is our impression from the limited number of examples of syphilitic arteritis in which we have tested for spasm that spasm was mixed with some occlusion and was not usually an especially striking phenomenon. In the arterial spasm of thrombo-angitis obliterans and Raynaud's disease, we do not yet know the primary cause of

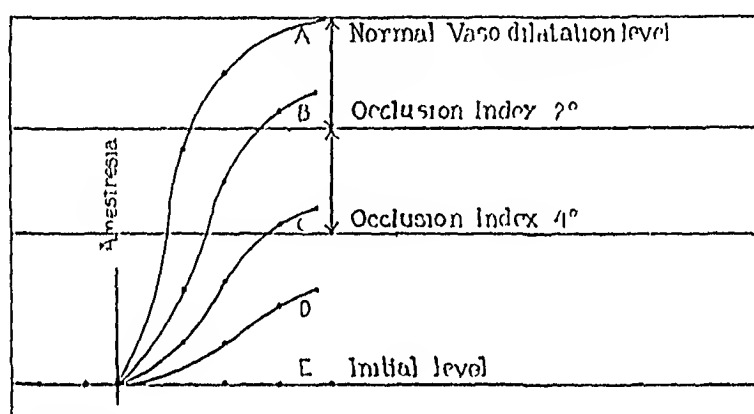


Fig 27—Response to anesthesia as a guide to treatment. If the surface temperature rises to the normal vasodilatation level, curve A, or to within 2 C (35.3 F) of this point (occlusion index less than 2 C), curve B, the treatment should be directed toward overcoming the spasm. If the rise in temperature is definite with an occlusion index between 2 and 4 C (39.1 F), curve C, the release of spasm may be of assistance. But if the rise in surface temperature is only to a point at which the occlusion index is more than 4 C, curve D, or if there is no rise, curve E, treatment should be for occlusion, sympathectomy is unjustifiable.

the reaction. Any information along this line will be gratefully received by all who are required to treat patients with vascular diseases in the extremity.

2 *Vasodilator Drugs*.—It is natural next to turn for assistance to the pharmacologic agents that cause vasodilatation or oppose sympathetic stimulation. We have tried out in this connection the nitrites, acetylcholine and ergotamine, but we have not been able to obtain an immediate effect on the peripheral vessels of the extremity in arterial spastic disease that at all approaches the interruption of the sympathetic fibers.

3 *Local Heat*.—In certain forms of arterial spasm, heat applied locally relaxes the spasm. This is particularly true in certain traumatic lesions. It is impossible to use readings of the surface temperature

directly as an index of the effect of local heat on the vascular circulation. We have studied in isolated instances the normal recovery from heat and cold, but have not yet established satisfactory criteria for the normal limits. The effect of local heat in arterial spastic disease is not as lasting as the application of heat to raise the body temperature.

4 *General Heat*—We have produced hyperthermia in these patients by two methods: (a) diathermy and (b) hot baths. Dr S. L. Warren supervised the diathermy treatments, which consisted in the passage of 5 amperes of high frequency current (wavelength 300 meters) through

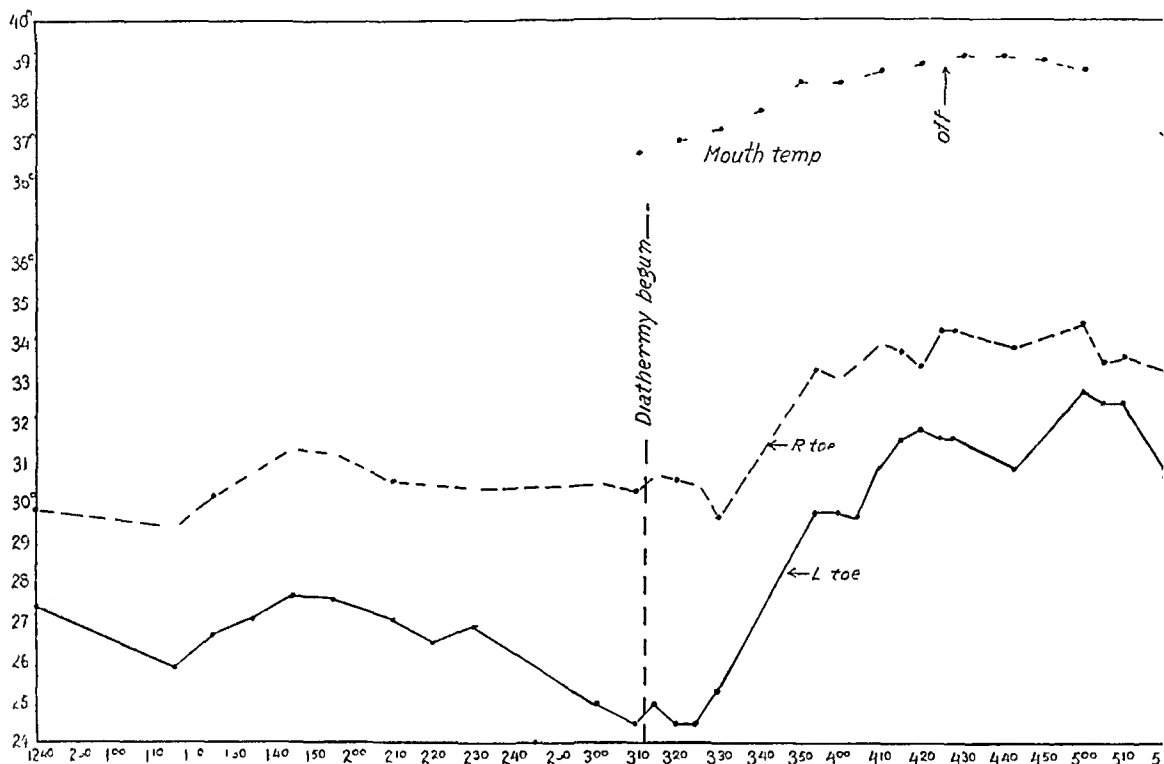


Fig 28—Arteriospasm, the effect of diathermy in Mr C B. Sympathectomy had been performed on the right side. Diathermy caused a rise in the mouth temperature and the surface temperature of the denervated side, but a much greater rise proportionately on the side not operated on. A difference of over 5 C (41 F) in the skin temperature of the two toes recorded at the beginning of treatment is reduced to 1 C (33.4 F). Note also that the surface temperature of the left toe is still elevated considerably above its initial point after the mouth temperature had returned to normal. Temperature of the room was 22 C.

the body between large electrodes. The continuous hot baths were given by the method recently advised by Mehrtens and Pouppirt¹⁶. In our cases both procedures caused a relaxation from arterial spasm which outlasted the hyperthermia produced (figs 28, 29 and 30). Pain was temporarily alleviated. We have not yet followed these patients long

16 Mehrtens, H. G., and Pouppirt, P. S. Treatment of Intermittent Claudication with Hyperpyrexia Produced by Baths, *J. A. M. A.* 95:1910 (Dec 20) 1930.

enough to determine how effective these measures will prove in permanently keeping the spasm under control. We believe, however, that they produce a much more desirable form of hyperthermia than that following foreign protein.

5 *Foreign Protein*—The injection of various types of foreign protein has long been used in the treatment for several conditions, among them the peripheral vascular diseases. Allen and Smithwick¹⁷ and Brown and Henderson¹⁸ have found considerable improvement following repeated injections of typhoid vaccine. The former workers have

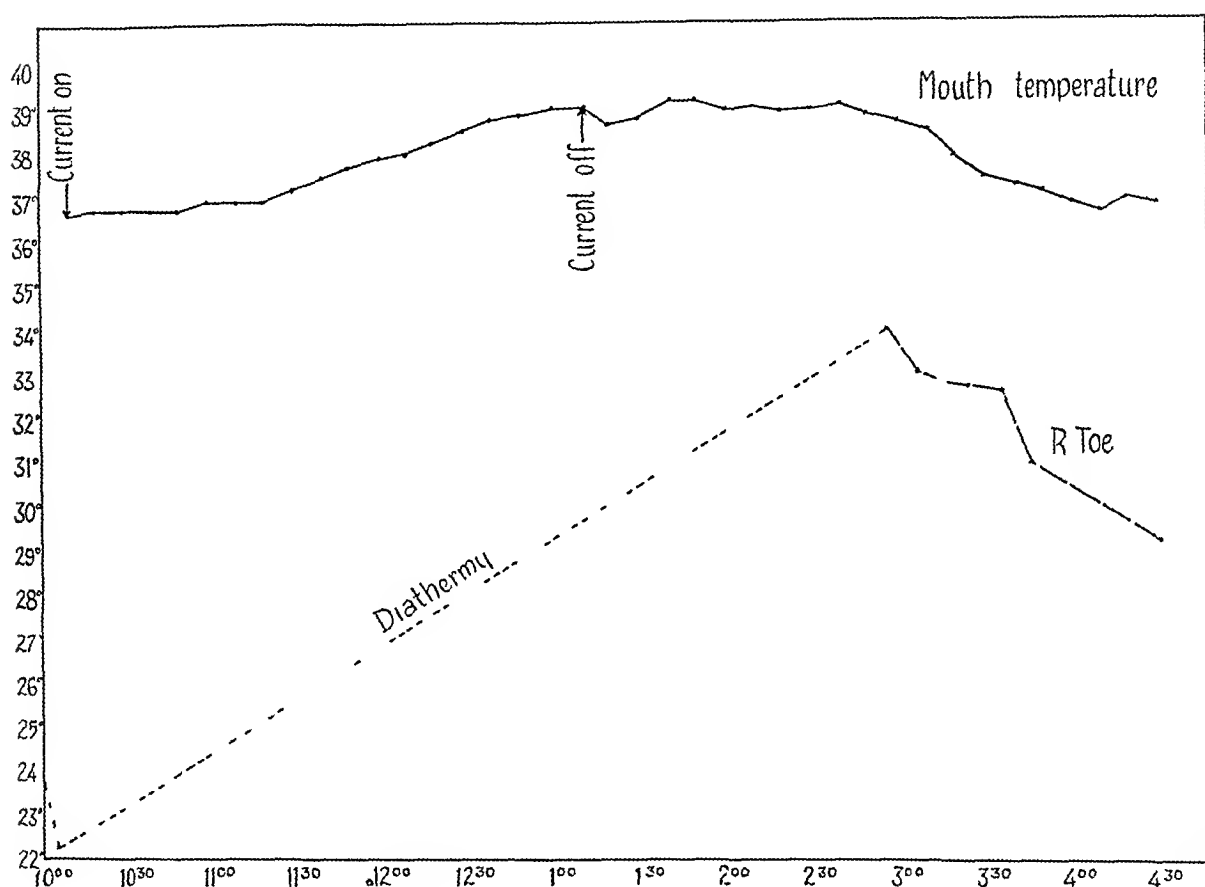


Fig 29—Arteriospasm the effect of diathermy in Mr F S. Note that the surface temperature in the toes is still elevated three hours after the diathermy was discontinued and after the mouth temperature had returned to normal. Temperature of the room was 25 C.

called attention to the danger of thrombosis with this method.⁵ Even though the effect may prove somewhat more persistent than that following hyperthermia produced by the methods already described, the

17 Allen, A W, and Smithwick, R H. Use of Foreign Protein in Treatment of Peripheral Vascular Diseases. Results of Intravenous Injections of Typhoid Vaccine, J A M A **91** 1161 (Oct 20) 1928.

18 Brown, G E, and Henderson, M S. The Diagnosis and Treatment of Arterial Vascular Disease of the Extremities, J Bone & Joint Surg **9** 613, 1927.

severity of reactions, whether or not associated with complications, makes it not an ideal form of treatment

6 *Surgical Interruption of Sympathetic Fibers*—Whenever vasoconstriction is demonstrated, it can be overcome by the interruption of the sympathetic fibers to the involved area. This may be done at different levels. The first attempt to accomplish this was periarterial sympathectomy. Leriche developed the procedure of denervating a length of artery by the removal of its adventitia. He thought that

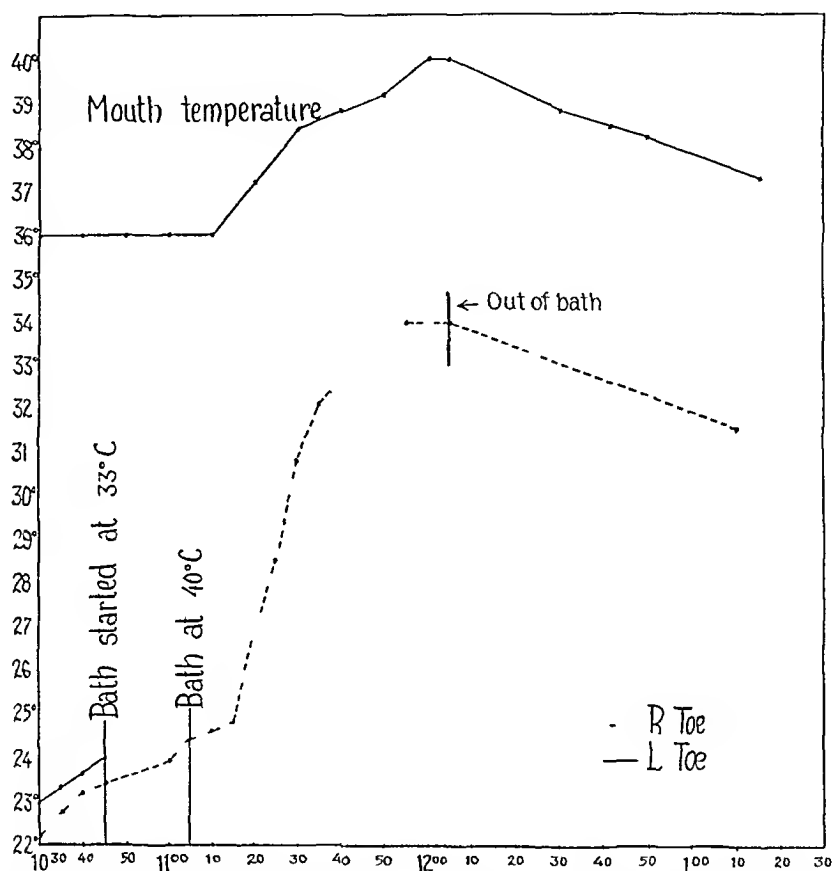


Fig 30—Arteriospasm the effect of a continuous hot bath in M₁ F S. Note the more rapid fall in mouth temperature than in surface temperature after the completion of the bath. Temperature of the room was 22.7 C.

thereby he interrupted efferent fibers to the peripheral field. Following this procedure it was reported that a vasodilatation occurred in the corresponding extremity. Later it was added that vasodilatation also occurred in other extremities, which was thought to be due to some type of reflex disturbance. More recently anatomic studies have verified the previous anatomic and physiologic conception that the vasoconstrictor fibers for distant fields are confined to the main nerve trunks. A study of the surface temperatures in the extremities after other simple operations, such as herniotomy, shows that some of these vascular

changes previously thought due to interruption of sympathetic fibers are merely nonspecific postoperative effects (fig 31) Possibly some of the results reported are due to interruption of afferent fibers Under any circumstance, it is quite clear that periarterial sympathectomy is not a satisfactory method of overcoming vasoconstrictor spasm in the extremities

7 Ganglionectomy—Approximately the same degree of vasodilatation that can be temporarily induced by anesthesia can be made permanent by sympathetic ganglionectomy in the proper area The duration of the effect has been questioned We have patients now that have maintained for more than two years a constant elevation to a

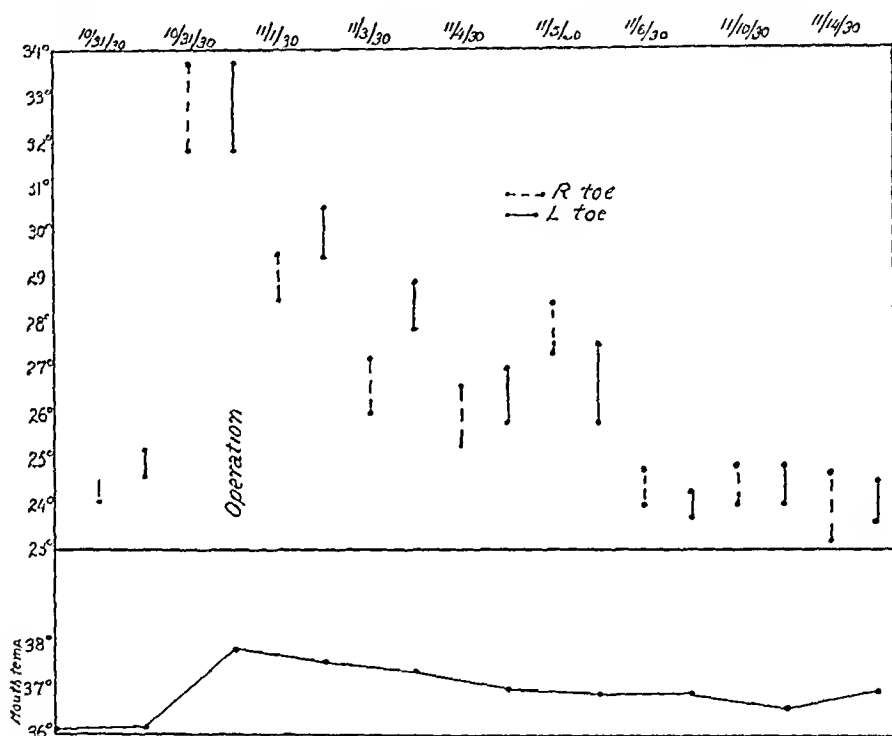


Fig 31—Nonspecific postoperative effect on peripheral circulation of normal vessels in C M, on whom hermiotomy had been performed on the right side Each line represents the maximum and minimum temperatures recorded under standard conditions (room temperature 20 C) for a period of one-half hour each day Note the marked elevation above the original level for several days following hermiotomy under local anesthesia

high level on the side on which operation was performed (figs 32 and 33) Brown and Adson,¹⁹ Filatov²⁰ and others reported similar

19 Brown, G E, and Adson, A W Physiologic Effects of Thoracic and of Lumbar Sympathetic Ganglionectomy or Section of the Trunk, Arch Neurol & Psychiat **22** 322 (Aug) 1929

20 Filatov, A Khnische und experimentelle Untersuchungen uber die Schwankungen der Hauttemperatur nach chirurgischen Eingriffen am lumbalen und cervicalen Abschnitte des sympathischen Nervensystems, Beitr z klin Chir **149** 95, 1930

effects, some over even a longer period. The influence of sympathectomy on the progress of the thrombotic process in the mixed group, as in certain cases of thrombo-angitis obliterans, is not known as yet. It is our belief that not only will the circulation be relieved of the spastic

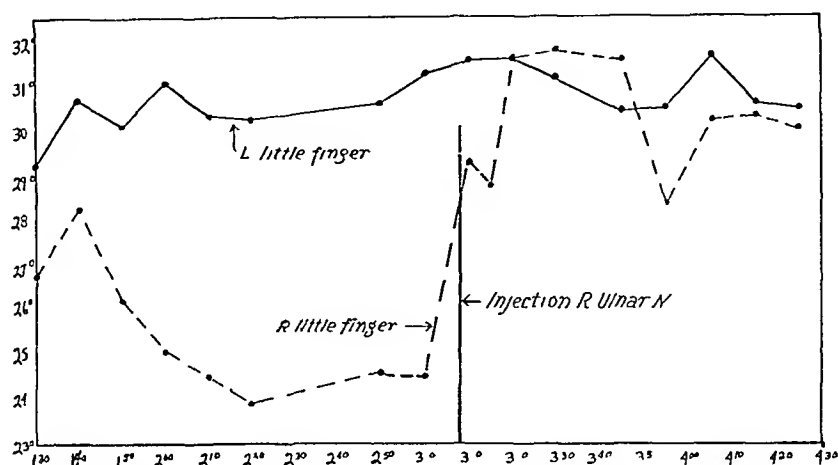


Fig 32—Left cervical sympathectomy three months previous to test in Miss L D. Surface temperature of the left fingers was maintained at a high level, which is the same level reached by the right little finger after the right ulnar nerve was blocked with procaine hydrochloride. Temperature of the room was 20.5 C.

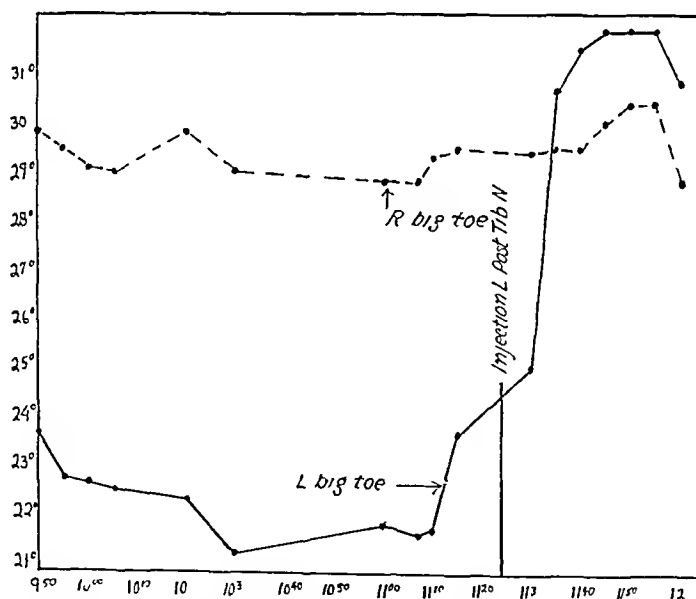


Fig 33—Thrombo-angitis obliterans twenty months after right lumbar sympathectomy in P B. Surface temperatures on the right side have been maintained at a high level continuously since operation (for twenty months when this paper was written), together with great improvement in symptoms on this side. The level maintained is a little below that reached by the left great toe after the left posterior tibial nerve was blocked with procaine hydrochloride. Temperature of the room was 20 C.

element, but the absence of spasm may exert a beneficial effect to retard extension of the thrombosis. Our opinion in this matter is based on the known development of thrombosis as a complication of the arterial spasm in the later stages of Raynaud's disease. It is also influenced by the possibility that reflex spasm of the vasa vasorum may be a factor in an extension of the disease. These considerations in regard to the further progress of the thrombotic element are at present theoretical, the effect of ganglionectomy in improving the peripheral circulation by removing arterial spasm is proved.

In some cases, particularly those in which pain is an important element in the disease, as Smithwick and White²¹ have pointed out, interruption of the peripheral nerve may be of benefit to overcome the pain and to release the arterial spasm in the peripheral area supplied. This is particularly applicable to older persons who should not be submitted to ganglionectomy and in cases in which hyperthermia by physical means is not advisable or proves insufficient. We have recently used alcohol injection into the peripheral nerve with great satisfaction in overcoming the painful excessive reaction to moderate cold in a case of causalgia.

In the mixed group, we do not yet have a sufficiently extensive experience to decide definitely the proportion of occlusion beyond which the results do not justify sympathectomy. As a tentative plan, we are not doing this operation if the occlusion index is over 4 degrees in the foot. We have seen improvement in the circulation of the foot after sympathetic denervation, with the progression of the thrombotic process in one or two toes to the point that local amputation of the latter was necessary. Thus we did not consider a reflection on the desirability of the sympathectomy.

In brief, as long as spasm is the dominant factor in the viability of the extremity, measures are mainly directed toward the overcoming of this vasoconstriction. We know that surgical interruption of the sympathetic fibers will effect this result promptly. Certain simpler methods, however, also do so temporarily. The exact value of the latter must be worked out by extensive studies. At present, the choice between conservative measures and an operation on the sympathetic system must be decided in each case separately. If spasm cannot be controlled by other measures, sympathetic ganglionectomy may be less radical than nonoperative treatment.

21 Smithwick, R. H., and White, J. C. Elimination of Pain in Obliterative Vascular Disease of the Lower Extremity (A Technique for Alcohol Injection of the Sensory Nerves of the Lower Leg), *Surg, Gynec & Obst* **51** 394, 1930.

COMMENT

This study of the sympathetic influence on the vascular system has brought to light a fundamental difference in the control of the peripheral and the splanchnic arteries. The usual surgical depth of general anesthesia entirely obliterates vasoconstriction in the extremities, while it scarcely affects that of the splanchnic area. This seems to be dependent on an anatomic or, more probably, a phylogenetic difference in the vasomotor control for these regions.

In the future, data based on this distinction of spasm and occlusion and a more minute study of these elements will greatly assist in settling many fundamental questions concerning peripheral vascular diseases. When and how in the occlusive group does obliteration of normal vasoconstriction occur? How does the arteriospasm of the spastic group differ from normal vasoconstriction in severity, in persistence or in what way?

SUMMARY

Pioneers have recently opened up important possibilities in the application of anatomic and physiologic knowledge of the sympathetic nervous system to several clinical syndromes. For the achievement of sound progress in this interesting field there is now needed the establishment of criteria by which to measure the sympathetic activity in the various systems. The effect of the temporary interruption of the extrinsic nerve supply to the large bowel by spinal anesthesia is offered as an index of the amount of sympathetic inhibition present in megacolon. For vascular diseases of the extremities, a simple, systematic test is outlined which distinguishes the effects of spasm and of occlusion. The vasoconstrictor stimuli to the area studied are interrupted by anesthesia the effect of which on the surface temperature is compared with the similar response of normal persons. We have established the normal levels for spinal, general and conduction block anesthesia. In an individual case, if anesthesia is accompanied by no elevation of temperature in the cool distal part of the extremity, occlusion without spasm is present, if the skin temperature reaches the normal vasodilatation level, sympathetic vasoconstriction is responsible for the circulatory symptoms and if the elevation is definite but not to this level, both occlusion and spasm participate. The difference between the highest temperature obtained and the normal vasodilatation level has been termed the occlusion index, as it measures the effect of organic obstruction to the peripheral circulation. Nerve block anesthesia is particularly useful in this vasomotor test on account of its simplicity and freedom from discomfort. In doubtful or borderline cases, its results should be checked with those of spinal or general anesthesia.

By these methods, valuable information in regard to the nature and the treatment of various types of vascular disease in the extremities is obtained. In the purely occlusive group some compensatory mechanism releases the collateral and terminal vessels from vasoconstriction when the local circulation is seriously reduced. This does not obtain in the spastic group.

The treatment for these two groups should be along radically different lines. The principle of that for purely occlusive disease is the obtaining of a more peripheral distribution of the reduced amount of blood available, while in spastic disease the treatment should be directed toward an augmentation of the local circulation by overcoming sympathetic vasoconstrictor spasm. Particularly valuable methods are hyperthermia, which produces temporary vasodilatation, sympathetic ganglionectomy for permanent effects and interruption of the peripheral nerves in cases in which ganglionectomy is desirable but contraindicated by the patient's condition.

ELECTROCARDIOGRAPHIC STUDIES OF THE EFFECT OF ANAPHYLAXIS ON THE CARDIAC MECHANISM*

LEO H. CRIEP, M.D.
PITTSBURGH

The present conception of anaphylaxis indicates that symptoms and death occur as the result of the mechanical irritation produced on the cells of the so-called shock organ by the interaction of antigen and antibody. This shock organ has been shown to differ with various animals. Thus, in the guinea-pig, it has been found to be the smooth muscle of the bronchi and bronchioles. A guinea-pig dying in anaphylactic shock presents a definite and characteristic group of symptoms, the most prominent of which is gasping for breath. The animal dies with its lungs in a state of maximal distention. These symptoms are due to a closure of the bronchi and bronchioles, so that while air may be taken into the lungs because the accessory muscles of respiration are brought into play, it cannot be forced out of the lungs. The guinea-pig, therefore, dies in acute asphyxia. In the rabbit, however, the shock organ is the media of the arterioles. In cases in which the fatal dose of protein is given in the vein of the ear of a sensitive rabbit, the first arterioles to be affected by the interaction of this protein (antigen) and the antibody are those of the pulmonary system. This interaction brings about irritation with subsequent constriction of these vessels followed by obstruction to the flow of blood through them and to the lung. The result is obvious lack of aeration of blood and, therefore, asphyxia, damming back of the blood into the right side of the heart with subsequent dilatation of that side, and congestive heart failure if death is delayed.

While the mechanism of anaphylactic shock in the guinea-pig and in the rabbit is fairly well understood, there is but little in the literature with regard to the series of changes occurring in the heart during anaphylaxis, particularly with reference to the disturbances in the cardiac mechanism. In 1910, by direct and graphic observations, Auer and Lewis¹ showed that various disturbances in conduction take place in

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¹ From the Departments of Physiology and Internal Medicine, the University of Pittsburgh.

¹ Auer, J., and Lewis, P. A. Anaphylaxis in the Guinea Pig, *J. Exper. Med.* **12** 171, 1910 (Plate IX, figure 5).

the guinea-pig during anaphylaxis. Königsfeld and Oppenheimer² carried this study further and demonstrated practically the same thing with the electrocardiograph, but they ventured the opinion that most of the findings were due to the asphyxia that anaphylaxis induces in the guinea-pig. In 1911, Auer,³ studying the heart of the rabbit during anaphylaxis by direct and graphic observation, reported the presence of heart block. In 1913, Auer and Robinson⁴ undertook a thorough electrocardiographic investigation of the heart of the rabbit during anaphylaxis, and they concluded that disturbances in conduction ranging from slight delay to partial and complete heart block are rather constant in this condition, suggesting that anaphylaxis may play a rôle in cardiac disturbances in man.

The present study was undertaken to establish electrocardiographically the series of changes in the heart of the guinea-pig and in that of the rabbit during anaphylaxis, and to determine whether the changes are due to a direct and specific influence of the anaphylactic process on the myocardium. For this purpose, we shall indicate the results obtained by the electrocardiographic studies of the guinea-pig in acute asphyxia and in anaphylaxis, and those obtained in the rabbit in asphyxia and anaphylaxis and in a condition artificially simulating that of anaphylaxis, namely, the state following clamping of the pulmonary artery.

EXPERIMENTAL WORK

EXPERIMENT 1—*A Electrocardiographic Study Following Artificial Asphyxia in the Guinea-Pig*—The following technic was used in the experiment.

For this study guinea-pigs weighing about 350 Gm. were used. In six animals the cardiac changes resulting from artificial asphyxia were demonstrated. The hair of both fore legs and the left hind leg was cut, and the legs were scrubbed well with soap and water and then with a hot saline solution. The guinea-pig was stretched on an animal board, and an electrocardiogram was taken with electrodes leading from the extremities. Following light ether anesthesia, the trachea was carefully exposed, and another tracing was taken. Asphyxia was subsequently induced by clamping the trachea. In two of the guinea-pigs tracings were made with indirect electrodes. In the remaining four, the chest was opened after the trachea had been clamped, and the nonpolarizable, direct electrodes of Noyen were employed. One electrode was placed in the region of the right

2 Königsfeld, H., and Oppenheimer, E. Elektrokardiographische Untersuchungen beim anaphylaktischen Shock des Meerschweinchens, *Klin. Wchnschr.* **1** 849 (April 22) 1922.

3 Auer, J. Lethal Cardiac Anaphylaxis in the Rabbit, *J. Exper. Med.* **14** 483, 1911.

4 Auer, J., and Robinson, G. Canby. An Electrocardiographic Study of the Anaphylactic Rabbit, *J. Exper. Med.* **18** 450, 1913.

auricle, the second in the region of the left auricle and the third touching the tip of the left ventricle. Tracings were thus taken with both indirect and direct electrodes, until cardiac standstill was observed.

The electrocardiographic tracings were practically the same for all animals, and therefore we shall tabulate the findings for only one. The tracings are from lead II and represent indirect leads unless otherwise indicated. The rate was 330 per minute, and was practically uninfluenced by ether anesthesia. Both auricles and ventricles were regular. The P-R interval was 0.05 second. The QRS complex was 0.03 second. The waves had the normal configuration and direction. T was positive in lead II (fig 1 *A* and *B*). The trachea was clamped with a hemostat and thirty seconds later, just as symptoms of asphyxia were beginning to appear, the heart rate slowed to 300 per minute. The T

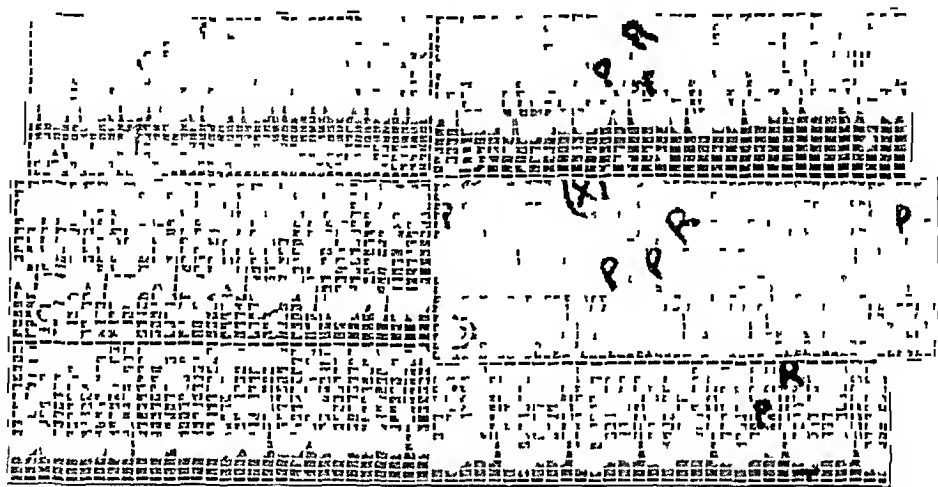


Fig 1—*A*, before anesthesia, the rate was 330, the P-R interval, 0.05 second. *B*, during anesthesia, the rate was 330. *C*, thirty seconds after the trachea had been clamped, the rate was 300, the P-R interval, 0.07 second, T, negative. *D*, transition from the normal mechanism (\downarrow), the auricular rate was 300, the ventricular rate, 150. *E*, 2:1 block, the auricular rate was 300, the ventricular rate, 150, three minutes later. *F*, the tracheal clamp had been released, the mechanism is normal.

wave became inverted in lead II and more pronouncedly so in lead III, and the P-R interval lengthened somewhat (0.07 second) (fig 1 *C*). The next observed change is seen in figure 1 *D* and *E*, the ventricular rate was still slower, 150 per minute, while the auricular rate was 300 per minute, the ventricles responding only to every second auricular contraction. The P-R interval was 0.1 second. Lead III shows the same changes, except that P is shown superimposed on T. When the tracheal clamp was released four and a half minutes after it was applied (fig 1 *F*), the normal mechanism was reestablished, only to give way

to 2:1 and later to 3:1 heart block on reapplication of the clamp (fig 2 *A* and *B*). Complete dissociation of auricles and ventricles, and a high T take-off are seen in figure 2 *C*. The ventricular complexes bear no relation to the auricular representative. The presence of complete heart block is better seen in figures 2 *D* and 3 *A*. These show a general tendency to a lowering of the ventricular rate, with an increase in the QRS interval and a more marked abnormality of this complex, showing its origin to be lower in the ventricles. Thus, figure 2 *D*, using direct leads, shows the following: The auricular rate was 180 per minute, the ventricular rate, 60 per minute, and the QRS complex, 0.2 second and bizarre, appearing not unlike that of a block of the right

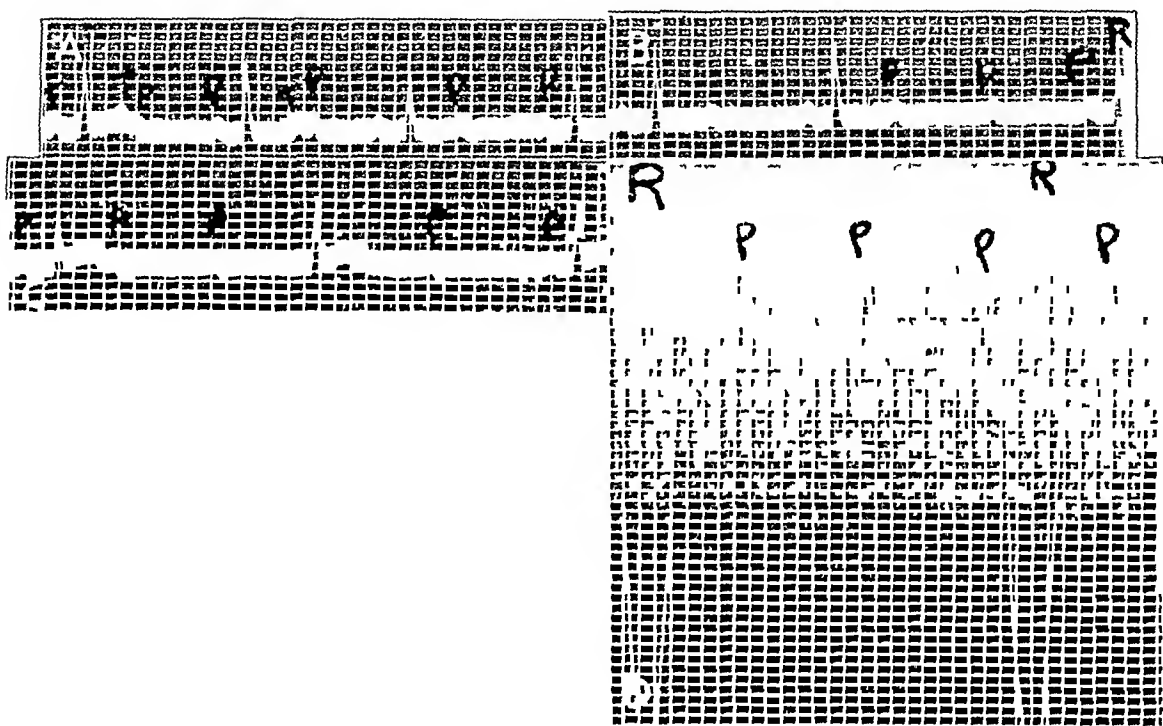


Fig 2—*A*, the trachea had been clamped again, there was a 2:1 block in one minute. *B*, partial 2:1 and 3:1 block, two minutes later, the auricular rate was 210, the ventricular rate, 90. *C*, there was complete heart block in four minutes, high T take-off. *D*, direct leads, there was complete heart block six minutes later, the auricular rate was 180, the ventricular rate, 60, the QRS complex, 0.2 second, there was a tendency toward a 3:1 block.

branch of the bundle. Subsequently the rate became much slower, so that in figure 3 *A* the auricular rate was 100 per minute, the ventricular rate, 20 per minute, and the QRS interval, 0.32 second. Somewhat later (fig 3 *B*), the auricles ceased beating rhythmically, so that they showed fibrillation, while there was still evidence of idioventricular rhythm, with a further increase in the QRS interval to 0.48 second. This was followed by auricular standstill (fig 3 *C*).

B Electrocardiographic Studies in Anaphylaxis in the Guinea-Pig —
The following technic was used

Guinea-pigs were passively sensitized to egg white by the intraperitoneal injection of 0.2 cc of an anti-egg rabbit serum of high titer (1:10,000). About twenty-four hours later anaphylactic shock was brought about by the intravenous injection of 0.3 cc of 50 per cent whole egg white. Electrocardiographic tracings were taken before the injection of egg white and during the appearance of anaphylactic symptoms, with both indirect and direct leads.

There was apparently nothing of note about the normal curve obtained during anesthesia. The rate was 300 per minute. The P-R

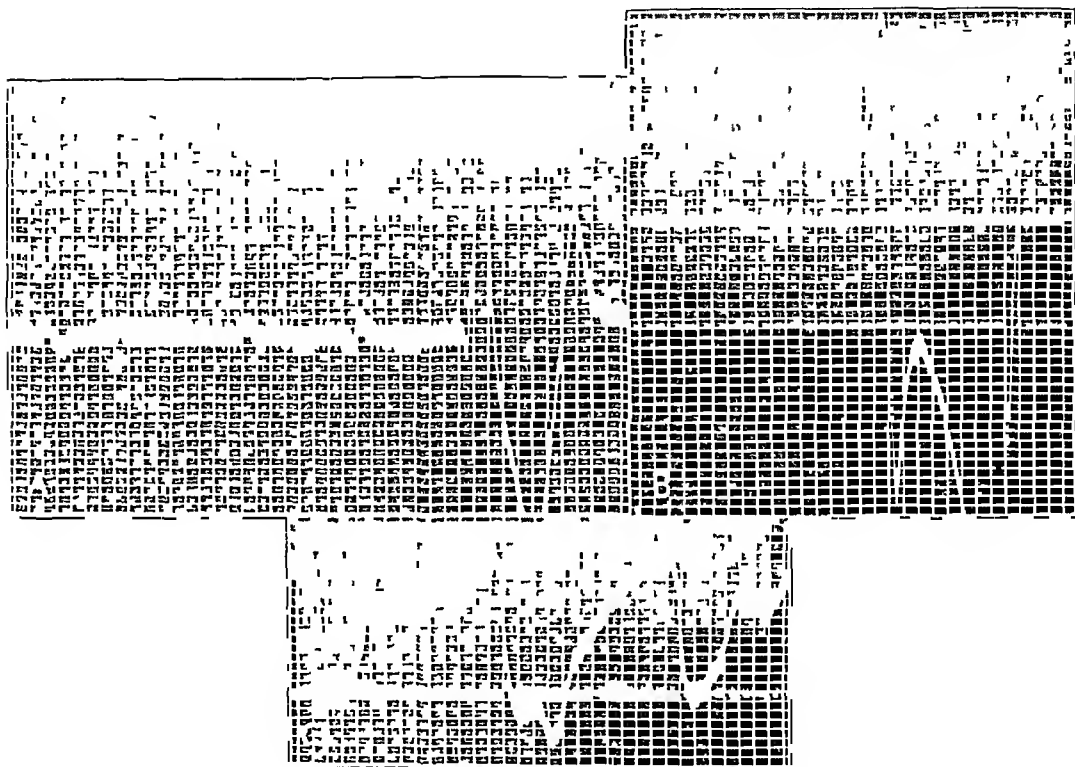


Fig 3—*A*, complete block, direct L, the auricular rate was 100, the ventricular rate, 20, the QRS complex, 0.32 second, there was an occasional auricular extrasystole. *B*, complete block, auricular fibrillation. *C*, ventricular fibrillation, followed by cardiac asystole.

interval was 0.04 second, and the QRS complex, 0.03 second. Arrhythmia was not evident (fig 4 *A*). Following the injection of egg white and the subsequent development of anaphylactic symptoms, certain progressive changes occurred. Thus, as figure 4 *B* shows, the rate was slowed with the subsequent establishment of 2:1 block, so that, while the auricular rate was 180 per minute, the ventricular rate was 90 per minute. This condition of "dropped beats" alternated with normal beats, during which the P-R interval was increased to 0.1 second. The

T wave became inverted (fig 4 C), the general tendency being toward 2:1 block with the rate still slower, the ventricular rate was about 75. The ventricles slowed down further, so that they beat about 30 per minute and independent of the auricles, a tendency toward 2:1 and 4:1 block. The T wave was negative in all leads, it took off below the line, and the R-T interval was short. Complete dissociation of rhythm

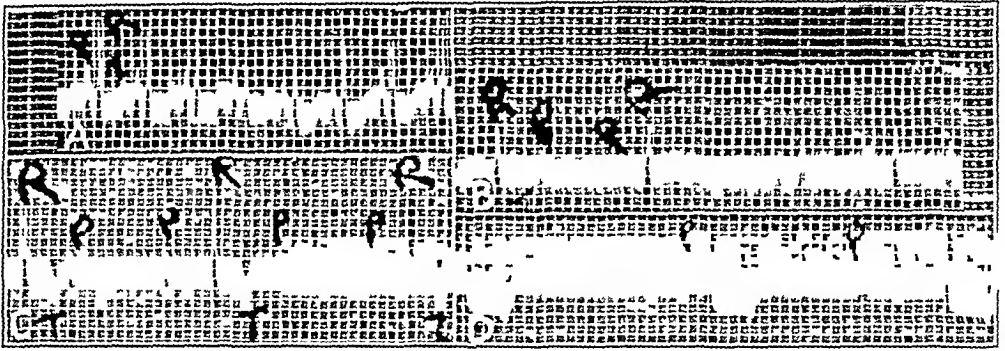


Fig 4—A, normal, rate, 300. B, anaphylaxis in one minute, 2:1 block, the auricular rate was 180, the ventricular rate, 90. C, inverted T, two minutes later, the ventricular rate was 75. D, complete block, three minutes later, the auricular rate was 90, the ventricular rate, 40.



Fig 5—A, complete block, three minutes later, paroxysmal ventricular tachycardia, 240, the auricular rate was 120, T, negative, with a low T take-off. B, the auricular rate was 60, there were long periods of ventricular asystole. C, ventricular fibrillation.

followed (fig 4 D). This condition became more marked, with evidence of branch bundle block (the QRS complex was 0.4 second), until, fourteen minutes from the development of the initial symptoms of anaphylactic shock, the auricles beat regularly while there were a series of ectopic ventricular beats and complete dissociation of rhythm. Ventricular fibrillation finally preceded cardiac standstill (fig 5).

EXPERIMENT 2—*A Electrocardiographic Study Following Clamping of the Pulmonary Artery of a Rabbit*—The following technic was used in the experiment

Electrocardiographic tracings were taken before and during light ether anesthesia in normal rabbits. The two fore legs and the left hind leg were cleaned of hair and scrubbed with a hot saline solution. Tracings were thus taken with indirect leads. The chest was opened, and artificial respiration was employed. An attempt was made to duplicate the condition of obstruction in the pulmonary circuit seen in anaphylaxis by clamping off the pulmonary artery. Tracings were again taken with direct leads, the nonpolarizable electrodes of Noyen being used, the electrodes were placed over the right auricle, the left auricle and the tip of the left ventricle.

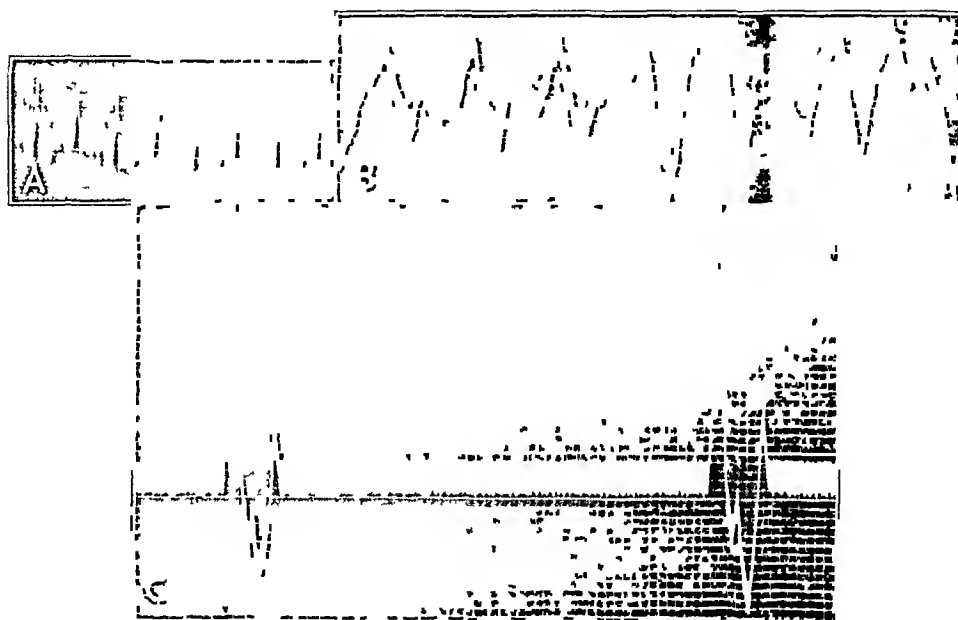


Fig 6—*A*, normal *B*, the pulmonary artery was clamped, there was ventricular fibrillation *C*, auricular standstill, the QRS complex was 0.28 second

The normal tracing showed nothing of note. Continuous tracings were taken. Almost immediately following clamping of the pulmonary artery, the ventricles began to fibrillate (fig 6 *B*). Space does not permit the inclusion of longer strips of these tracings, but they show various degrees of disturbed cardiac mechanism ending in auricular and ventricular fibrillation. The sequence of these various disturbances in mechanism was not always the same. This apparently was due to the time interval between tracings, or to the condition of the muscle of the heart. The foregoing analysis does show, however, that clamping the pulmonary artery produces relatively sudden and profound changes in the cardiac mechanism in the rabbit.

B Electrocardiographic Studies Following Artificial Asphyxia in the Rabbit—Artificial asphyxia was produced in several rabbits by clamping the trachea. Tracings were taken with indirect and direct leads as described.

There were no appreciable changes before or during ether anesthesia. The rate was 360 and regular. The P-R interval was 0.06 second, the QRS complex, 0.03 second. T was positive in lead II (fig 7 A). When the trachea was clamped (fig 7 B), there was a definite slowing of ventricular rate to 120 per minute, and a tendency toward nodal rhythm. However, two minutes later, and apparently without any explainable cause, normal mechanism was established (fig 7 C), with slight ventricular predominance and a definite increase in the P-R interval to 0.1 second. T was still positive in leads I and II. Shortly afterward (fig 8 A), there was a further increase in the P-R interval to 0.12



Fig 7—A, normal tracing, rate, 360, P-R interval, 0.06 second, QRS complex, 0.03 second. B, the trachea had been clamped, there was nodal rhythm, rate, 120, T, positive. C, three leads, normal mechanism (two minutes), P-R interval, 0.12 second, there was a right ventricular predominance.

second, with a sudden change in the character of the QRS complex, two minutes later nodal rhythm was reestablished, only to give way (fig 8 C) to an antemortem type of fibrillation and cardiac standstill.

C Electrocardiographic Study of Anaphylaxis in the Rabbit—The following technic was used:

In order to study the effect of anaphylactic shock on the heart of the rabbit, several rabbits were actively sensitized with egg white, the technic suggested by Coca and Grove being employed. "A primary intravenous injection is made of 0.5 cc of 50 per cent egg white (first day), on the sixth day 5.0 cc of whole egg white are injected intraperitoneally, on the eleventh day and on the succeeding seven days 1.0 cc of whole egg white is injected intraperitoneally. The animals are allowed to rest one week and then receive 4 or 5 cc of undiluted whole egg white subcutaneously. On the sixth day thereafter serum is obtained from each animal and the precipitating titer is determined by layering dilutions of whole egg

white over the undiluted serum in the conical ring test tubes Rabbits whose serum shows a titer of over 1 to 5000 or more as a rule are good subjects for anaphylactic shock" This was induced by the intravenous administration of 5 cc of 50 per cent egg white Tracings were taken before and during shock immediately after the onset of the initial symptoms of anaphylactic shock

Auricular fibrillation was seen (fig 9 B) T_2 became negative, and only a few seconds later, 2 1 heart block appeared (fig 9 C) Thirty

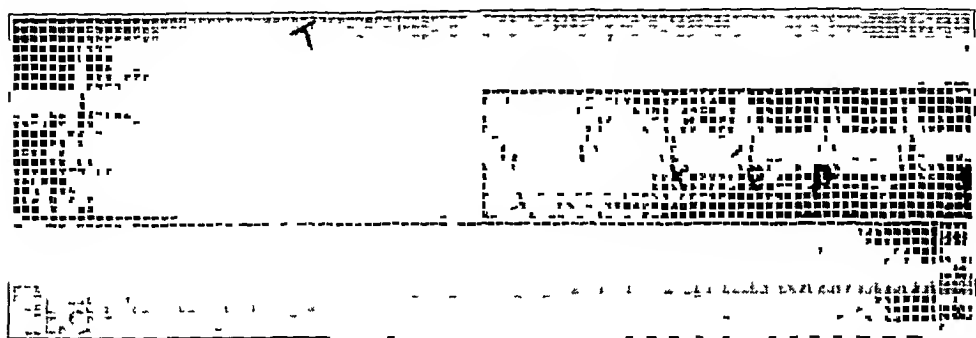


Fig 8—A, continuous with figure 1 C, delayed conduction B, rate, 120, nodal rhythm, two minutes later C, ventricular fibrillation

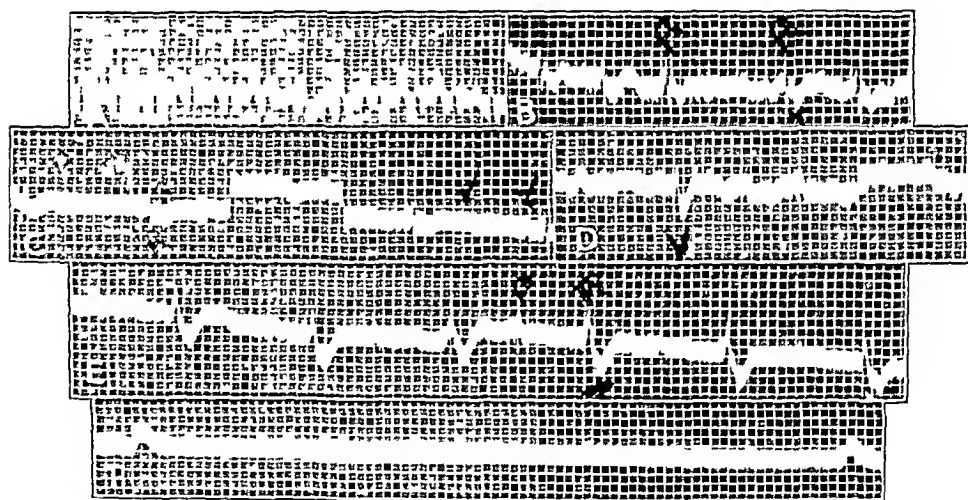


Fig 9—A, normal, rate, 360, P-R interval, 0.06 second B, anaphylaxis, auricular fibrillation, rate, 180, T_2 negative C, continuous with figure 1 B, rate, 110, 2 1 block D, auricular fibrillation, ventricular rate only 15 E, delayed conduction, rate, 110, QRS complex, 0.06 second, T, negative, P-R interval, 0.24 second F, auricular standstill for five minutes, ventricular rate, 15, irregular

seconds later, the auricles were still fibrillating (fig 9 D), but the ventricular rate was only 15 per minute This condition changed to that seen in figure 9 E, which shows the ventricular rate to be 110 The P-R interval was 0.24 second, or almost four times longer than normal T was inverted in lead II Complete block followed, and,

finally, five minutes later (fig 9 F), there was complete auricular standstill accompanied by a slowly and irregularly beating ventricle at the rate of about 15 per minute

PATHOLOGIC SECTIONS OF THE HEART AND LUNGS IN GUINEA-PIGS AND RABBITS

Examination of sections of the heart during anaphylaxis did not show definite pathologic changes Dr Mortimer Cohen, of the department of pathology of the University of Pittsburgh, furnished sections of the heart and the lungs of guinea-pigs and rabbits that died during anaphylaxis for study Sections of the heart showed nothing of note Sections of the lungs of guinea-pigs showed definite constriction of the bronchi and bronchioles with some degree of emphysema Those of the lungs of rabbits showed a marked constriction of the pulmonary arterioles

COMMENT

From an analysis of the electrocardiograms obtained from the artificially asphyxiated guinea-pig and from the guinea-pig during anaphylaxis, it appears that the profound changes in cardiac mechanism are analogous in the two conditions One notes in both a similar and definite train of events (1) slowing of the rate with normal mechanism, (2) the appearance of partial heart block, followed by total block, branch bundle block, occasional nodal rhythm, auricular fibrillation, ventricular fibrillation and paroxysmal ventricular tachycardia, and (3) either auricular or ventricular asystole, followed by cardiac standstill It is interesting to point out that practically all of the tracings taken during asphyxia and anaphylaxis showed an inversion of the T wave in lead II, with a shortened R-T interval and the T wave starting either above or below the line In the rabbit, the cardiac changes following acute asphyxia, anaphylaxis or clamping of the pulmonary artery are essentially the same, that is, the picture is that of profound myocardial involvement accompanied by disturbed rhythm, leading finally to cardiac death It appears, therefore, that the disturbances in the cardiac mechanism are more or less similar during anaphylaxis in both the guinea-pig and the rabbit, in spite of the fact that the pathologic physiology of anaphylaxis differs in the two species Although death in the guinea-pig is due to a constriction of the bronchi and bronchioles with inability to expire the air from the lungs, while in the rabbit it is due to constriction of the pulmonary arteries and arterioles with damming back of blood into the right side of the heart and circulatory failure, this difference in the mode in which anaphylaxis proves fatal in the two species bears no influence on the resulting cardiac disturbances as revealed by the electrocardiogram The cardiac changes

in both animals must be due primarily to interference with the blood supply to the heart, that is, myocardial anoxemia, although cerebral anoxemia is, no doubt, also a factor. This is shown to be true by the fact that with restoration of ventilation normal mechanism is reestablished (fig 1 *F*). The abnormal mechanism described is therefore due to the factors presented and not to the specific effect of anaphylaxis as thought and described by Auer.⁵

The myocardium and the conducting mechanism are affected not only by the state of anoxemia referred to, but also by the irritating effect of lactic acid and the various katabolites that have been demonstrated to exist in asphyxia.⁶ Thus disturbances in rhythm occur long before there is any mechanical interference with the circulation.⁷

The exact rôle played by the vagus nerve in producing the cardiac changes discussed in this paper is not clear. While it has been demonstrated experimentally that stimulation of the vagus nerve may produce various forms of arrhythmia, the impression of various workers, notably Roaf and Sherrington,⁸ Sherrington,⁹ Matheson,¹⁰ and Lewis and Matheson,¹¹ seems to be that the influence of the vagus nerve is not very important, for its removal by atropine or section does not interfere with the occurrence of heart block.⁴ Furthermore, similar results are obtained in the spinal animal in which the cardioinhibitory center is absent.

SUMMARY

1. Electrocardiographic changes in the guinea-pig are analogous in artificial asphyxia and anaphylaxis.

2. The changes consist of bradycardia, partial and complete block, inversion of the T wave, with a shortened R-T interval and a high T take-off, and auricular and ventricular fibrillation.

3. The changes in the T wave are not unlike those noted in coronary occlusion and suggest the possibility that disturbances in the cardiac mechanism may be due to myocardial anoxemia.

5 Auer, J. Ueber den plotzlichen anaphylactischen Tod beim Kaninchen, *Zentralbl f Physiol* **24** 957 (Jan 7) 1910.

6 Kaya and Starling. *J Physiol* **39** 346, 1909. Sherrington. *J Physiol* **38** 381, 1909. Fletcher and Hopkins. *J Physiol* **35** 247, 1906-1907.

7 Robinson, G. Canby. *Am J Physiol* **31** 18, 1912-1913.

8 Roaf and Sherrington. *Quart J Exper Physiol* **3** 209, 1910.

9 Sherrington. *J Physiol* **38** 375, 1909.

10 Matheson, G. C. The Cause of Heart Block Occurring During Asphyxia, *Heart* **2** 55, 1910-1911.

11 Lewis, Thomas, and Matheson, G. C. A-V Heart Block as a Result of Asphyxia, *Heart* **3** 47, 1910-1911.

4 The foregoing conclusions are also true of the rabbit during asphyxia, during anaphylaxis and in a condition following clamping of the pulmonary artery

5 Microscopic sections of the hearts of guinea-pigs and rabbits revealed nothing of note as a physical basis for the changes observed

6 The vagus nerve does not seem to play an important rôle in the production of the disturbances in mechanism

7 The functional cardiac changes observed in the guinea-pig and rabbit during anaphylaxis are not specifically due to the anaphylactic state, but rather to the state of asphyxia that anaphylaxis induces

Dr C C Guthrie gave helpful suggestions, and Mr J Lawler gave technical assistance in the preparation of some of the material for this paper

1004 May Building

SUBACUTE MENINGOCOCCAL ENDOCARDITIS *

NORMAN B GWYN, M D

TORONTO, CANADA

Imitating Libman, who prefers the term subacute streptococcal endocarditis to that of subacute bacterial endocarditis when speaking of the more chronic *viridans* type of infection, I have ventured to make use of the title presented, in connection with a case of infective endocarditis of long duration. This I do the more readily, first, because the classic picture of subacute bacterial endocarditis was so faithfully reproduced over a course of many months, secondly, because the meningococci were the only organisms isolated in culture from the blood and spinal exudate, and, finally, because I had the further good fortune in the consideration of this case to be able to submit the history and specimens to Dr Libman who, being more familiar with the occasional case of subacute bacterial endocarditis due to organisms other than *Streptococcus viridans*, was able to give me much necessary and useful information about these less common forms of infection.

There are doubtless many objections to be urged against the employment of a new term, and it is realized that the familiar picture of subacute bacterial endocarditis has become something which in one's mind is usually associated with infection by *S viridans*, yet it is to be remembered that *Bacillus influenzae*, *Staphylococcus aureus* and the gonococcus, are credited with the production of a certain small percentage of those cases labelled subacute bacterial endocarditis and running a more or less typical course, so that it is therefore probable that other organisms will be found capable of giving rise to the same set of symptoms and physical signs.¹

That this is a possible viewpoint seems to be indicated by the article of de la Chappelle,² who reported a case presenting all the features of

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¹ From the service of Dr Duncan Graham, Toronto General Hospital, and reported with his permission at the Section of Medicine of the Toronto Academy of Medicine

¹ Horder, T J. *Bacillus Influenzae* as a Cause of Endocarditis, Tr Path Soc London **57** 58, 1906. Libman and Cellar. Observations on the Etiology of Sub-Acute Infective Endocarditis, Tr A Am Physicians **25** 5, 1910. Smith, F J. The Influenza Bacillus as a Cause of Fatal Endocarditis After Eight Years (?), Lancet **1** 1201, 1908. Simons, I. Critical Review Bacterial Endocarditis, Quart J Med **7** 291, 1913-1914. Libman. M Clin North America **2** 117, 1918. Marmorstein, M. Contribution a l'etude des aortites grippales, Rev de med **28** 267, 1918.

² de la Chappelle. Am Heart J **4** 732 (Aug) 1929

subacute bacterial endocarditis, yet yielding only *Brucella abortus* in cultures before and after death, he referred also to other cases³ of endocarditis associated with *Brucella* infection, cases which, in one instance at least, were suggestive to a degree, with their early history of rheumatic fever and mitral disease and their subsequent course, of long drawn out infection with multiple embolic accidents. It is quite evident that the authors reporting some of these early cases hesitate to imply that *Brucella abortus* can behave like *S. viridans* in causing a chronic endocarditis resembling the subacute bacterial form, de la Chappelle, however, does not seem to be so conservative in his ideas, and on reading his contribution one is tempted again to suggest that the old rheumatic valve lesion may freely invite invaders other than *S. viridans* and *B. influenzae*, invaders that may adapt themselves to the more chronic form of warfare, represented by a prolonged course, embolic accidents, enlargement of the spleen, clubbed fingers, pigmentation of the skin and an abundant growth of vegetation on the valves. Whether or not one will find that these invaders provoke quite the same response in the tissues as do the streptococci of the *viridans* type cannot yet be stated. Such lesions as the Biacht-Waechter bodies in the heart muscles and the peculiar reaction in the kidneys may well be something not produced by every form of irritant or infection, and the question may be raised whether in these less common types of cases a previous *viridans* infection may not have died out, allowing other organisms to be found as late saprophytic invaders of the blood stream. This would seem unlikely and, in a few instances at least, immunologic reactions in the serum have pointed clearly in the other direction. Three distinct diseases, a chronic rheumatic and a subacute *viridans*, followed by a third, an acute meningococcus infection (as in the case to be reported), and all localized on the same heart valve would seem an anomalous condition indeed.

Endocarditis of an acute form has long been recognized as a complication of meningococcus meningitis. The reports of Cecil and Soper,⁴ and Warfield and Walker⁵ are interesting in that they were the first to detail acute meningococcus endocarditis occurring in the absence of meningitis "meningococcal septicemia with involvement of the heart valves." These cases have been more properly considered as acute bacterial endocarditis, running a course as they did of twenty-four days and six weeks,

3 Scott. Am J M Sc **175** 66, 1928. Evans, A. C. Hygienic Laboratory Bulletin, 1925, p. 143. Marlow, F. W. Meningococcemia J A M A **92** 619 (Feb. 23) 1929.

4 Cecil, R. L. and Soper, W. B. Meningococcus Endocarditis, with Septicemia, Arch Int Med **8** 1 (July) 1911.

5 Warfield and Walker. Bull. Ayer Clin. Lab., Pennsylvania Hospital, 1903, no. 1, p. 81.

respectively, the same could be said of the case reported by Drought and Kennedy⁶ and of most of the recorded instances of meningococcus endocarditis. Wright and Mackerwell,⁷ however, described an endocarditis of sixteen weeks' duration in which they found meningococci in the vegetations on the mitral valve, this case might well be called, in point of time at least, subacute bacterial endocarditis, while MacMahon and Burkhardt⁸ stated that in their case of meningococcus endocarditis the appearance of the patient was such that the diagnosis of subacute bacterial endocarditis was suggested, although the course of the infection and the Janeway spots were more in keeping with the acute form of the disease. In Morgan's⁹ two patients with meningococcal septicemia, both of whom recovered after an illness of three and four months, the history and physical findings were strangely suggestive of the subacute form of bacterial infection of the heart valves, with the observations on the blood, the prolonged fever and the crops of nodes. It is possible, as Herrick¹⁰ suggested, that many of the curious examples of chronic meningococcal blood stream infections which have gone on to cure have been subacute or chronic cases of meningococcus endocarditis which have become spontaneously bacteria-free, in general, however, the picture of a subacute bacterial endocarditis has not often been simulated by a meningococcal infection, and the history here given may therefore be of interest.

REPORT OF A CASE

Mrs. H., aged 37, had been attending the outpatient department for eight months, complaining of headache and pain in the chest. The diagnosis of subacute bacterial endocarditis had been made as a result of finding fever, a large heart, a loud systolic murmur in the mitral area and a diastolic murmur in the aortic area, together with the facts that the spleen and liver were both enlarged, that the fingers were clubbed and that the skin had the café-au-lait color so often spoken of as being present in this disease. It had also been noted that from time to time small petechiae had appeared in the skin and that there had been present albuminuria with casts and red blood cells on microscopic examination. The patient had been under constant observation and on three occasions had been found unconscious. There had been no determination, however, of the cause of the unconsciousness.¹¹ A few days before her admission to the hospital, headache had become quite severe and signs of meningitis developed, she complained of pain in her joints and it was noted that again there was a crop of petechiae. There were at this time several tender spots on her fingers which suggested Osler

6 Drought and Kennedy. Cerebral Spinal Fever, London, A & C Black 1919

7 Wright and Mackerwell. J Roy Army M Corps **25** 353, 1915

8 MacMahon and Burkhardt. Am J Path **5** 197 (May) 1929

9 Morgan. Bull Johns Hopkins Hosp **32** 245 (Aug) 1921

10 Herrick, W W. Extrameningeal Meningococcus Infections, Arch Int Med **23** 409 (April) 1919

11 Cerebral embolism was suspected

nodes. She was in the ward for two weeks, during which time two blood cultures were positive for meningococci and lumbar puncture brought away cloudy fluid from which meningococci were cultivated on four different occasions. It was interesting to note that in spite of the general infection the white blood count remained low, ranging between 6,000 and 12,000. The petechial eruption was profuse, albumin was present in large amounts and, as in previous examinations, there were numerous casts and blood cells in the urine. There was increased intracerebral pressure as was indicated by the distinct edema of the optic disks, she remained, however, clear up to within two days of her death, and presented at all times a picture more in keeping with the *meningitis* subacute form of bacterial endocarditis, so that I was surprised to a degree to find that I was dealing with an infection due to the meningococcus. Whether this was the organism that had initiated the illness eight months previously might, according to the arguments already made use of, be a matter for debate. Dr Libman, however, seemed willing to accept the evidence as presented, and certainly the course of the disease and the postmortem findings conform to what one had been used to consider as making up the picture of subacute bacterial endocarditis.

Autopsy,¹² performed a few hours after death, demonstrated that there was, as expected, a diffuse meningo-encephalitis affecting the brain and spinal cord. From the exudate, produced by the inflammation, meningococci were easily cultivated. The spleen was large, weighed 360 Gm and showed several infarcts. The liver was enlarged and both kidneys were large, both kidneys showed a pale red cortex, the glomeruli were prominent and there were fresh and old infarcts in both organs, the right kidney weighed 170 Gm, the left, 195 Gm. There was nothing striking in the other organs save the evidence of a terminal lobular pneumonia in both lungs.

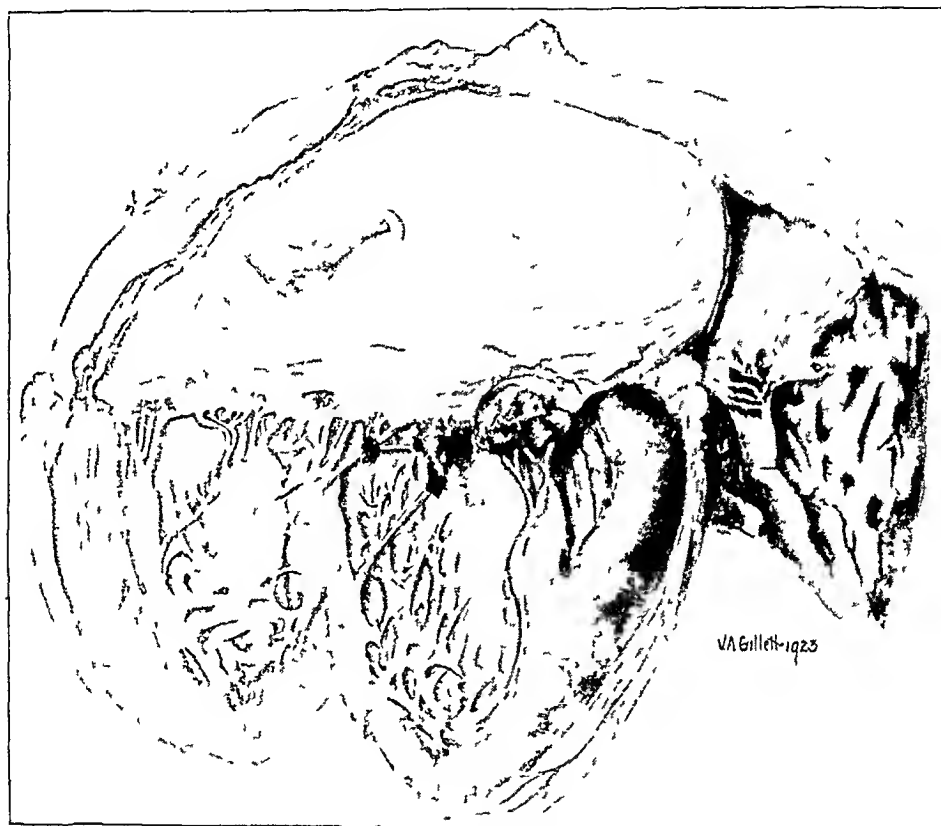
The heart, of course, was the organ in which I was most interested and I was fortunate in getting a water color reproduction at the time of the autopsy (see figure). The picture reproduced therefrom shows the moderate degree of enlargement of the left ventricle and the dilated left auricle, together with the thickening of the mitral valve and the shortening and retraction of the chordae tendineae, so indicative of an earlier rheumatic infection. At one point of the mitral valve marked destructive ulceration is present, and the granulations characteristic of the endocarditis are well depicted. The aortic valve was clear. Nothing grew in cultures from the vegetations on the valves.

Sections were made of the mitral valve and of the heart muscle and were reported on as follows: "The section shows about 1 cm of the valve curtain including its free edge. There is a marked nodular thickening present which involves the distal 8 mm of the cusp and rises abruptly to a maximum height of 6 mm from the outer surface. The apex of this nodule bears a crater-like area of ulceration measuring 4 mm at its mouth and 3 mm in depth. The disrupted surface is overlaid with a ragged incrustation of thrombotic material rich in polymorphonuclear leucocytes and containing many blue staining clumps of bacteria, the morphology of which could not be accurately made out. The vegetation is composed largely of fibrous tissue. At the base this tissue is of the mature variety rich in collagen and having scanty slit-like nuclei, while around the ulcerated area the growth is more cellular and resembles granulation tissue. Between these two extremes is a wide area of oedematous connective tissue which contains many blood vessels engorged with erythrocytes. The inflammatory

¹² Pathologic and bacteriologic records are from the service of Professor Klotz.

reaction present in and around the ulcerated area has infiltrated widely the interstices of the surrounding fibrous tissue. Deep to the area of ulceration interrupted masses of polymorphonuclear neutrophiles extend right through to the septal surface of the cusp where the endothelium is disrupted for a short distance. There is unmistakable evidence here of healed lesions which preceded the angry looking acute ulcerative process now present.

"Section of the myocardium shows the presence of an acute inflammation characterized by the presence of a few polymorphonuclear cells between the muscle bundles, and oedema of the interstitial tissue. There is also some scarring along the vascular channels indicative of a chronic myocarditis. This moderate perivascular sclerosis is diffuse and in many instances is nodular. The picture is very



Subacute meningococcus endocarditis

suggestive of rheumatic infection but no Aschoff bodies can be seen. Professor Klotz was of the opinion that the old condition was probably rheumatic though unable to make a positive diagnosis."¹³

As stated, both kidneys were large and pale, with a reddened cortex. The glomeruli were prominent and there were many small infarcts in evidence. The kidney sections seemed to show that an acute nephrosis had been engrafted on an acute interstitial and acute diffuse glomerulonephritis. The report as received from the Pathological Department of the Toronto General Hospital reads as follows: "Many acute foci of inflammation were present in the inter-

¹³ The report on the valve sections and heart muscle was made by Dr. Klotz and Dr. T. H. Belt.

stitial tissue and there was a diffuse involvement of the glomeruli. In addition a well marked degenerative process was present in the tubular epithelium. The whole picture evidenced an acute lesion, there being no fibrous change. The focal inflammatory lesions were perivascular, located in close relationship to both large and small vessels. There were more and larger infiltrations in the subcortical regions, where the arterial supply divides, than in either cortex or medulla. The polymorphonuclear leucocyte was the chief cell taking part in the reaction. The focal lesions were confined almost entirely to the interstitial tissue but occasionally they invaded tubules giving rise to small cellular casts within the denuded lumina. Not infrequently the inflammation was seen in intimate relationship to the afferent arterioles of the glomeruli and in such instances the adjacent group of tubules were often completely hyalinized and necrotic. The glomeruli were large and uniform in appearance. The capsular spaces were dilated but, for the most part, free from wandering cells. The glomerular tufts were swollen and presented a striking cellular increase, not only did they contain a number of leucocytes but the clothing endothelium had undergone a proliferative change. The loops were devoid of blood. Bowman's capsules were not thickened but occasionally showed some exfoliation. There was no fibrous proliferation anywhere to indicate a subacute or chronic process. Diagnosis (1) acute diffuse glomerulonephritis, (2) acute interstitial nephritis (focal), (3) acute nephrosis."

In a personal communication, Dr W. L. Robinson said that this kidney picture is not incompatible with the diagnosis of subacute bacterial endocarditis.

COMMENT

In the foregoing report, there is little deviation from the classic picture of subacute bacterial endocarditis. We have suggested that the possibility of an earlier *viridans* infection of the valves be considered. In the final summing up, an infection which may have died down only to be supplanted by one due to the meningococcus. It must be remembered, however, that the history given was one of a continuous febrile illness of eight months' duration. A determination as to the time at which one infection might have ceased and another begun is therefore impossible. If two distinct infections had been in existence, one must reckon with the fact that at no time did they produce a different set of symptoms. Meningitis may be the terminal accident in a case of chronic *viridans* endocarditis, as has been pointed out by Smith and Brumfield¹⁴. In the case reported by these writers, the meningitis was apparently due to an infection by *S. viridans*. In the present case, I had the feeling that *S. viridans* would be found as the infecting agent in the meningitis which finally developed. One point of interest must be touched on. From the beginning to the end of this patient's illness, there was a constant appearance of the Osler nodes rather than the Janeway spots. This must always be held to suggest the subacute and chronic infection as opposed to the more acute type.

14 Smith and Brumfield. Am Heart J 2 446 (April) 1927

It is now recognized that infection by the meningococci may assume a very chronic form, the possibility that those chronic septicemias may mean that the meningococci have lodged on a heart valve must always be thought of. Many of these chronic meningococcal septicemias have gone on to cure without showing signs of involvement of either brain or endocardium, and after months of positive blood cultures. The disappearance of organisms from the blood stream may indicate the spontaneous cure of an endocarditis, such as is occasionally recorded in cases of subacute bacterial endocarditis due to *viridans* infection. Such recoveries seem to occur with considerable frequency in the course of these meningococcal septicemias, and it would appear that if the brain and spinal cord are not attacked, recovery may follow even without antimeningococcus serum.

It is not necessary at this moment to discuss these chronic meningococcal septicemias. A large literature is growing up on the subject. Among many articles to be referred to are those by Bloedorn,¹⁵ Weichselbaum and Ghon,¹⁶ Rhoads,¹⁷ Bray,¹⁸ Montgomery,¹⁹ Bourdelles,²⁰ Dock,²¹ Finlay and Rhea,²² Hay and Huyck,²³ Andrewes,²⁴ Cabot,²⁵ and Vesell and Barsky.²⁶ Herrick's suggestion that these chronic septicemias may represent an endocarditis has been referred to. The description of Morgan's cases leads one inevitably to suggest that an endocarditis was present. His descriptions are those of cases of subacute bacterial endocarditis as one is used to seeing them. It is possible that in the present case, recovery might have ensued if the brain and spinal cord had not been attacked.²⁷

15 Bloedorn. *Am J M Sc* **162** 881, 1921

16 Weichselbaum and Ghon. *Wien klin Wchnschr*, 1905, p 24

17 Rhoads. *Am J Path* **3** 623, 1927

18 Bray, H. A. Chronic Meningococcus Septicemia Associated with Pulmonary Tuberculosis, *Arch Int Med* **16** 487 (Sept) 1915

19 Montgomery. *Canad M A J* **20** 266 (March) 1929

20 Bourdelles. *Presse med* **36** 660, 1925

21 Dock, W. Intermittent Fever of Seven Months' Duration Due to Meningococcemia, *J A M A* **83** 31 (July 5) 1924

22 Finlay and Rhea. *Tr A Am Physicians*, 1912, p 381

23 Hay and Huyck. *Canad M A J* **19** 695 (Dec) 1928

24 Andrewes F. W. *Lancet* **1** 1172 (April 28) 1906

25 Cabot, Richard. *New England J Med* **201** 139 (July 18) 1929

26 Vesell and Barsky. *Am J M Sc* **179** 589 (May) 1930

27 Since the writing of this article, there has appeared the report by Master, of New York, on "Meningococcemia with Endocarditis" (*J A M A* **96** 164 [Jan 17] 1931). Three cases were reported in which the prolonged temperature, embolic accidents and cardiac signs suggested endocarditis. In all three cases meningococci were cultivated from the blood, antimeningococcus serum was used and recovery took place.

SUMMARY

1 A case is reported that for eight months showed symptoms and physical signs which one is accustomed to associate with infection of the heart valves by *Streptococcus viridans*—subacute bacterial endocarditis

2 Blood cultures in the last two weeks of the illness were positive for meningococci

3 Death took place as a result of invasion of the brain and spinal cord by the meningococci

4 The observations at autopsy agree closely with those described as occurring in association with subacute bacterial endocarditis. Meningococci were recovered at autopsy from the meninges only. The lesions in the heart and kidney as described were apparently in accordance with those observations recorded at autopsy in cases of subacute bacterial endocarditis

EFFECTS OF EXERCISE ON EXPERIMENTAL CARDIAC INFARCTION¹

DON C SUTTON, M D
AND
MILTON D DAVIS, M D
CHICAGO

Although extensive experimental studies have been made of the effects of ligation of the coronary arteries, apparently no review of the effects of exercise following experimental cardiac infarction has been made

Knowledge of the effects of exercise at varying intervals after ligation should give information that could be transferred to the treatment of human beings Accordingly a series of experimentally produced infarcts in dogs was studied as to the effects of regulated exercise

Kolster¹ observed dogs living seventeen months after ligation of the ramus descendens anterior Miller and Matthews² kept dogs alive for ninety days after ligation of the left coronary artery Both described infarcts, and Miller and Matthews² observed marked thinning of the ventricular musculature near the apex

Smith³ observed the electrocardiographic changes following ligation of the ramus descendens anterior in dogs living up to sixty-three days He is the first author to mention the effects of exercise, but gives no accurate data as to the amount or duration of the exercise

In clinical literature reference is frequently made to the coincidence of hypertrophy in the presence of an occlusion of the coronary artery or of cardiac infarction Experimentally, Stewart⁴ observed cardiac hypertrophy after producing injury of the heart muscle by the injection of epinephrine hydrochloride MacCallum⁵ stated that sufficient experimental evidence is lacking on this point because of many other factors involved that may also cause hypertrophy Eyster⁶ believed that "the

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¹ From the Department of Physiology and Pharmacology, Northwestern University Medical School

1 Kolster Skandinav Arch f Physiol 4 1, 1893 cited by Porter

2 Miller, J L and Matthews, S A Effect on the Heart of Experimental Obstruction of the Left Coronary Artery, Arch Int Med 3 476 (June) 1909

3 Smith, F M Ligation of Coronary Arteries, Arch Int Med 22 8 (July) 1918

4 Stewart, H J J Clin Investigation 3 475, 1927

5 MacCallum, W G Textbook of Pathology, ed 4, Philadelphia, W B Saunders Company

6 Eyster, J A E Tr A Am Physicians 42 13, 1927

question of physiological hypertrophy from simple cardiac stimulation or increased cardiac work due to muscular exercise is still an open one," and added that much of the experimental work is contradictory. It has been shown recently by Herrmann and Musser⁷ that after the production of experimental pericarditis with adhesions, some hypertrophy always resulted. If these adhesions were relieved by a second operation, little hypertrophy occurred.

METHODS

In this study five dogs were used, each of which was trained to run on a motor-driven treadmill at a constant speed of a little over 3 miles an hour at an incline of 15 degrees. The training period extended over at least five days, and the time of each run was gradually increased until the dog was able to run for from thirty to sixty minutes with little or no signs of fatigue. Throughout this work a protocol of each run was recorded. These dogs were prepared according to the method described by Sutton and King.⁸

The operation was done aseptically, ether anesthesia and artificial respiration being used. An incision was made in the third left intercostal space, and the fibers of the pectoralis major muscle were separated with minimum injury. The pericardium was incised, and the ramus descendens anterior was ligated, usually from 1 to 2 cm from its origin. X-ray photographs were taken before and again immediately after the operation. The x-ray technic and that of measuring the films was the same as that followed by Eyster.⁶ Exposures of less than a second were taken at the end of inspiration, with a distance of 1 meter from the target to the film. The diastolic size of the heart as recorded on the x-ray plates was measured with the planimeter.

Exercise was started on the treadmill from two to six days after the ligation. The frequency of the exercise and the amount were increased in each succeeding dog as it was learned how much work the animal could endure. Any cardiac changes were followed by x-ray photographs, and the animals were weighed at frequent intervals.

RESULTS

After ligation in dog 2 (table 1), a six day rest period was allowed before exercise was started. The first run was for fifty minutes, and no signs of fatigue appeared. Thereafter exercise was given for from fifty to sixty minutes every fourth day for forty-four days. This animal was killed and an autopsy performed on it on the seventieth postoperative day. There were fibrous adhesions over the anterior surface of the left ventricle, and all that remained of the infarcted area was a small puckered area of fibrosis at the apex. The wall at this point was not thinner than normal.

Three animals were given exercise on the third postoperative day. The first (dog 4, table 2) had run ten minutes on the first day of exercise when fatigue and weakness made further exercise impossible.

⁷ Herrmann, G, and Musser, J. H. *Am Heart J* 4 268, 1929.

⁸ Sutton, D. C., and King, W. W. *Proc Soc Exper Biol & Med* 25 842, 1928.

As the days passed, more and more exercise was possible, so that within nine days this dog could run for sixty minutes with relatively little fatigue. The exercise period was fixed at one hour, and experiments were conducted every second or third day for three weeks, during which time no discomfort was noticed. On the ninety-eighth day this dog was

TABLE 1—*Dog 2*

Time of Examination	Diastolic Area of Heart in X Ray Plate, Sq. Cm	Pulse Rate	Running Period, Min	Fatigue	Weight, Kg	Comment
Before operation	73.3	96	50	+	16.0	
After operation	63.0					
22 days	69.1	72	50	+	13.0	
27 days	68.5	80	55	++		
31 days	64.7	100	60	+	13.6	
44 days	68.1	112	60	+		
53 days	73.5	108			12.7	
65 days	70.6	76			13.8	
70 days	70.0	112			13.7	Killed, autopsy performed
Percentage of change	-5%				-15%	

TABLE 2—*Dog 4*

Time of Examination	Diastolic Area of Heart in X Ray Plate, Sq. Cm	Pulse Rate	Running Period, Min	Fatigue	Weight, Kg	Comment
Before operation	65.6	96	30	+	16.8	
After operation	55.8	124				
3 days	63.7		10	++		
4 days	65.4	134	8	+++		
5 days	61.5	124	30	++	13.0	
7 days			28	++		
9 days			60	+		
12 days			50	+		
14 days			45	++		
18 days			55	+		
20 days			50	+	11.6	
24 days			60	+		
30 days			55	++	10.0	
33 days			65	+		
44 days	59.0	76				
48 days			60	++	10.0	
53 days	59.9	80			10.5	
63 days					10.0	
65 days	61.9	96				
76 days			60	+	11.6	
80 days	62.5	92				
91 days					13.0	
97 days	54.4	104			12.0	
98 days						Killed, autopsy performed
Percentage of change	-15%				-29%	

sacrificed, and autopsy showed extensive noninfectious pericardial adhesions extending from the site of the ligation to the apex. The apex was thin (from 2 to 3 mm) in thickness and was replaced by a fibrous tissue scar, which was clearly demarcated on the endocardium. This scar included the base of the posterior papillary muscle and extended to the base of the anterior papillary muscle.

The second dog (dog 6, table 3) in this group ran sixty minutes on the third day and every two or three days thereafter for three weeks, with no signs of distress. Beginning on the two hundred twenty second postoperative day, rigorous exercise (from seventy to ninety minutes) was again resumed daily for two weeks. At no time was there any evidence of fatigue or other cardiac symptoms. Throughout this period the weight and the general condition had been practically constant, but after the three hundred second day the animal rapidly lost weight, refused food and died in the cage on the three hundred nineteenth day. Firm adhesions over the entire distribution of the ramus descendens anterior were found at autopsy. Near the apex anteriorly the ventricular muscle was replaced by markedly thinned fibrous tissue (3 by 4 cm

TABLE 3—Dog 6

Time of Examination	Diastolic Area of Heart in X Ray Plate, Sq. Cm	Pulse Rate	Running Period, Min	Fatigue	Weight, Kg
Before operation	54.6	84	50	+	10.6
After operation	*				
3 days	55.0	108	60	+	
12 days	53.0	76	60	+	
17 days	52.0	108	65	+	9.7
30 days	54.8	116			
39 days	56.2	84			
52 days	54.7	80			
67 days	55.4	96			11.0
78 days	55.6	116			12.7
84 days	53.6	112			11.7
96 days	52.9	108			10.5
109 days	47.0	116			10.0
222 days	52.0	108	90	+	9.7
236 days	46.1	108	60	+	
259 days	47.4	124			9.0
311 days	43.8	126			7.0
Percentage of change	—20%				—34%

* No film taken

in thickness), forming a well defined scar. There was no suggestion of an aneurysm from the outside, nor from the x-ray pictures, but on section this thinned area showed a well defined aneurysmal sac. The ramus descendens anterior was completely obliterated in a mass of adhesions at the site of the ligation. One x-ray picture of this dog (see figure) showed bulging at the apex, which was interpreted as an aneurysmal bulging.

In the third group of two dogs, exercise on the treadmill was started on the second day following the operation and continued for forty-five and fifty minutes, respectively. These dogs ran almost daily for periods of from forty-five to seventy minutes for the first three weeks. On the eighth day one dog had a severe attack, giving every indication of undergoing extreme pain. Exercise on the following day again caused a similar attack, but this condition could not be produced

again. This animal died in the cage on the hundred thirty-fifth day, and extensive adhesions were found over the anterior surface of the heart. There was a clearly defined area of fibrosis demonstrable in the endocardium near the apex, including a part of the base of the posterior papillary muscle and some of the anterior papillary muscle. This area was 25 mm in width by 30 mm in length and from 1 to 2 mm in thickness. Although no bulging was noticed in the intact heart, on sectioning there was a definite outpouching of the endocardium. The second dog in this group died after the thirtieth day, unfortunately, no autopsy was done.



X-ray picture of dog 6 showing thinning and bulging of the apex

COMMENT

The amount of work that the average laboratory dog can perform until exhausted on the treadmill is variable. Previous training and psychic factors probably play an important rôle. From thirty to sixty minutes of running on our treadmill never appeared to cause any appreciable fatigue in the dogs in this series. Subsequent work has shown that a normal dog can run the entire afternoon with only a five minute rest period per hour.

The estimation of fatigue is purely an arbitrary matter. The ease with which the animal exercised before operation was compared with the postoperative runs. The dog having the six days' rest (dog 2) was not exercised severely as to the length of the runs or as to their frequency.

The extensive anastomosis of the superficial coronary arteries can be seen quite easily just under the epicardium of the left ventricle. Miller

and Matthews,² Karsner and Dwyer⁹ and others have pointed out that because of this extensive anastomosis the scar resulting from ligation is much smaller than the area supplied by the ligated artery. Our findings are in agreement with this statement, the myocardial scar varying greatly as to size even though all the ligations were approximately at the same level. We wish to emphasize the consistent occurrence of anastomosing vessels on the left ventricle between the descending branches of the circumflex and the lateral twigs from the ramus descendens anterior. Thus it is often necessary to ligate one of these anastomosing vessels also in order to obtain a good-sized scar. This extensive anastomosis prevents the formation of a large scar and makes possible a better functional recovery following ligation.

It is frequently stated that exercise increases the work of the heart, and that this leads to hypertrophy. The literature contains considerable evidence supporting the theory of work hypertrophy and some evidence denying it. Our observations show that the body weight and adhesive

TABLE 4—*Relation of Cardiac Area and Body Weight in This Series of Dogs*

Dog	Change in Cardiac Area	Change in Body Weight	Days Lived
2	5% decrease	15% decrease	70
4	15% decrease	29% decrease	98
6	20% decrease	34% decrease	319
12	1% increase	7% decrease	23
13	9% increase	3% decrease	135

pericarditis are two factors of prime importance, which must be controlled before any conclusions can be drawn concerning the occurrence of cardiac hypertrophy following the ligation of the ramus descendens anterior.

Table 4 shows that in two cases the increase in cardiac area was slight. Stewart¹⁰ and Eyster¹¹ stated that a variation of more than 10 per cent must occur before one should conclude that there is any real change in the size of the heart. The three remaining dogs showed a decrease in cardiac area each of which was accompanied by a distinct fall in body weight. Simonds and Brandes¹² recently found that in starvation the heart loses weight in about the same proportion as the body as a whole. If we assume from this that there may also be a decrease in the cardiac area, we have evidence in three cases at least that there is a similar decrease in cardiac area with a loss in body weight.

⁹ Karsner, H. T., and Dwyer, J. E. *J. M. Research* **34** 21, 1916.

¹⁰ Stewart, H. J. *J. Clin. Investigation* **7** 339, 1929.

¹¹ Eyster, J. A. E., Meek, W. J., and Hodges, F. J. *Cardiac Changes Subsequent to Experimental Aortic Lesions*, *Arch. Int. Med.* **39** 536 (April) 1927.

¹² Simonds, J. P., and Brandes, W. W. *Effect of Experimental Hyperthyroidism and of Inanition on Heart, Liver and Kidneys*, *Arch. Path.* **9** 445 (Feb) 1930.

In this series there was no marked enlargement of the pathologic heart resulting from exercise (table 4). At the beginning of this work it was thought that the formation of a large scar in the myocardium *per se* might result in cardiac hypertrophy because of the extra load thrown on the remaining healthy cardiac tissue. Regardless of this and the additional work to which these hearts were subjected by exercising, the results do not appear to favor this point of view. It is evident that the body weight must be kept constant throughout the experiment before one can conclude that there is any change in cardiac area due to hypertrophy as determined from the x-ray photograph.

Adhesive pericarditis was a constant finding at autopsy, and this has been presumed to be a causative factor in producing cardiac hypertrophy. Thus, there are two factors, exercise and adhesions, which may play a rôle in producing hypertrophy, while the loss of body

TABLE 5—*Changes in Cardiac Area in Dogs During Ether Anesthesia*

Dog	Time		Cardiac Area, Sq. Cm.	Pulse Rate	Decrease, per Cent
E-1	1 45	Normal	52.9	92	
	2 00	Started ether			
	2 30	During ether	46.1	120	
	2 40	Stopped ether			
	2 50	X ray	45.8	128	14
	4 10	X ray	50.0	100	
	48 hr later	X ray	56.0	96	
E-2		Normal	49.2	120	15
		After	41.9	144	

weight, on the other hand, may cause an actual decrease in the size of the heart.

Effect of Ether and Operations on Size of Heart—It was noted that several times there was a decrease in the cardiac area immediately following the operation. Stewart¹⁰ advanced several explanations to account for this, among which tachycardia, reflex and direct stimulation of the heart, increase in the vascular bed and diminution of the blood volume are to be considered. The rôle that ether as an anesthetic plays in causing the aforementioned mechanism was investigated by anesthetizing two normal dogs and following the changes in the cardiac area.

It is questionable whether we can attribute any postoperative change in cardiac area to handling or ligating the coronary arteries themselves.

SUMMARY

A rest period of six days after infarction resulted in a small, well contracted scar without thinning of the ventricular wall in one dog.

In the remainder, exercise, within three days after operation, resulted in thin scars with aneurysmal bulging.

Although there is some variation in the x-ray silhouette from time to time, it is noted that the final average shows no evidence of hypertrophy or of dilatation

Adhesive pericarditis did not cause hypertrophy

Ether alone apparently causes a decrease in the cardiac area for several hours

CONCLUSIONS

Apparently rest after myocardial infarction results in the production of a small, firm scar, while early exercise results in a thin, bulging scar. The hope was entertained of proving this more definitely as a clinical fact, but evidently the reserve of a normal young dog's heart is infinitely greater than that of an arteriosclerotic heart.

Myocardial infarction per se does not cause hypertrophy.

Dr. A. C. Ivy gave assistance and encouragement in this work.

PRIMARY CARCINOMA OF THE LUNGS

PATHOGNOMONIC SIGNS IN THE DIAGNOSIS

JACOB POLEVSKI, M D

NEWARK, N J

The diagnosis of carcinoma of the lungs still constitutes to the practicing physician a baffling situation with which he is inadequately prepared to grapple. The general practitioner must have, if he is to succeed diagnostically, some definite signs or a definitely pathognomonic symptom complex to go by in meningitis, the headache, the Kernig sign and the rigidity of the neck, in pneumonia, the respiratory grunt and the peculiar disturbance in the pulse respiration ratio, in typhoid, the leukopenia, the rose spots and the slow pulse. One can enumerate even so many other conditions that have become diagnosable by the general practitioner because of the definite pathognomonic signs that they offer.

To these diagnosable conditions more and more disease entities are added as more and more pathognomonic signs and symptoms are elicited as time goes on. To the many conditions that as yet offer to the practitioner nothing fairly pathognomonic belongs carcinoma of the lungs. I have gathered this impression from my personal experience as well as from a careful perusal of the literature on the subject.

In 1904, Sehit¹ compiled from the literature 210 cases, of which only 6 were diagnosed during life. In 1923, Wells² found in Cook County Hospital 11 cases of primary carcinoma of the lungs with only one correct diagnosis. In 1925, Kilkuth³ found that at the Eppendorf Hospital in Hamburg only 34 per cent of 246 cases were diagnosed during life. As late as 1927, Fried⁴ had the following to say:

In primary carcinoma of the lungs signs are amazingly scant as compared with the amount of tissue involved and the grave character of the lesion. Again often they are ambiguous. Indeed, there is not a single symptom or a group of

¹ Submitted for publication, March 9, 1931.

² From the Department of Medicine of the Newark Beth Israel Hospital.

1 Sehit. Beitrag zur Kenntnis der primären Lungencarcinom, Inaugural Dissertation, Leipzig, 1904.

2 Wells, H. G. Relation of Clinical Diagnosis of Cancer and Value of Existing Cancer Statistics to Necropsy, J. A. M. A. **80** 737 (March 17) 1923, Cancer Statistics as They Appear to Pathologists, *ibid* **88** 399 (Feb 5) and 476 (Feb 12) 1927.

3 Kilkuth, W. Ueber Lungencarcinoma, Virchows Arch. f. path. Anat. **225** 107, 1925.

4 Fried, B. M. Primary Carcinoma of the Lungs, Arch. Int. Med. **40** 340 (Sept) 1927.

symptoms which is not common to tuberculosis as well as to cancer, or other chronic pulmonary conditions. In brief, it appears that there is no clinical signs which taken alone, would make the diagnosis of a primary neoplasm in the lung certain.

The rate of incidence of primary carcinoma of the lungs is on the increase, which according to the consensus, is actual and not merely due to the greater frequency in the diagnosis. This fact is borne out by the autopsy observations of many eminent pathologists both here and abroad. So little definite is as yet known concerning the possible cause of the increase that it is futile to go into the various theories advanced.

According to Kilkuth,³ whose necropsy material extended over a period of thirty-five years (1889-1923), primary carcinoma of the lungs represented 9.5 per cent of all the cases of carcinoma in the pathologic institute of the Hamburg Eppendorf Hospital. In 1923, the number of cases of pulmonary carcinoma equalled one-third the number of cases of carcinoma of the stomach found at autopsy at his large institution. In spite of this increasing incidence of pulmonary carcinoma, Fishberg⁵ stated that 80 per cent of his patients were sent in with the diagnosis of other pulmonary diseases, even though most of them were observed in other hospitals before admission to the institution with which he is affiliated. The same author insisted, though, that a diagnosis can be made by a careful history and physical examination, and that a very skilful percussion will reveal to the expert ear the fine distinction between the dulness of massive tuberculous involvement and the flatness of carcinoma. He also stated that the amphoric breathing audible in cavernous tuberculosis is usually heard in the mammary region or over the suprascapular region, while in carcinoma with a cavity it is heard over the sternum or the interscapular area. It has been my experience, though, that tuberculous cavities respect no area, while they may favor some. There is no question that the very skillful clinician may, possibly, differentiate between extreme dulness and flatness, and thus may make a diagnosis when others fail. But what about the average general practitioner who must have something more tangible, more pathognomonic? Can the diagnosis of carcinoma of the lungs be made within reach of the rank and file?

In a previous communication,⁶ I described a pathognomonic symptom complex that can be elicited, wholly or in part, in the vast majority of cases of primary pulmonary carcinoma. This symptom complex consists of a peculiarly characteristic history and definite physical signs.

5 Fishberg, M. Diagnosis of Pulmonary Neoplasm, *Arch Int Med* **37** 745 (June) 1926.

6 Polevski, J. Diagnosis of Primary Carcinoma of the Bronchus, *M J & Rec* **129** 448 (April 17) 1929.

The eliciting of this complex, in my opinion, will enable the average practitioner in a large majority of cases, to arrive at a correct diagnosis. Of the 6 consecutively diagnosed cases to be described, 2 were diagnosed by the intern.

CHARACTERISTIC HISTORY

In cases of carcinoma, if uncomplicated by coexisting tuberculosis, which situation prevails in many cases, the following is the history. The patient of cancer age, frequently of suggestive appearance, most often states that up to a reasonably short period of time prior to his present complaint he has not been troubled with any pulmonary difficulty. Dr James F Percy⁷ of Los Angeles, who has had a vast experience with cancer, emphasized further this strikingly negative previous history of patients with cancer. In his experience, these cases evince a history that is unusually free from previous infection in any part of the body.

The condition is ushered in, as far as the patient is concerned, in numerous yet characteristic ways. Some patients state that since an attack of bronchitis or pneumonia, which affected them from a few months to two years prior to their visit to the office, they have never been well, but have, more or less continuously, suffered from some pulmonary difficulty. Some patients state that they have had more than one attack of pneumonia, which has recurred at very short intervals within recent date. This last history is very suggestive. "As the rule is once pneumonia in pulmonary carcinoma always pneumonia for obvious reasons."⁸

In some cases the condition sets in more insidiously, until the more severe symptoms prompt the patient to seek medical advice.

Pain is the most frequently elicited complaint, and more than any other symptom draws the attention of the patient to his condition.

Hemorrhage is not uncommon. It may occur without warning or may develop insidiously.

Dyspnea, next to pain, is the most frequent complaint that brings these patients to the physician. This too, may develop gradually or may occur suddenly. Occasionally it is ushered in in the form of an asthmatic paroxysm. It may be caused by the final plugging of a bronchus, by the frequently complicating pleural effusion or by a unilateral phrenic paralysis with the resultant partial pulmonary collapse.

Any or all of these complaints in a patient of cancer age, particularly with a negative pulmonary history up to that age, are extremely suggestive and are frequently sufficient to justify a tentative diagnosis of primary pulmonary carcinoma.

⁷ From a personal conversation with Dr James Percy.

⁸ Statement made by Professor Erdheim of Vienna.

The characteristic physical signs consist of

- a* A high position of the diaphragm on the affected side
- b* Paradoxical respiration with a seesaw movement of the diaphragm
- c* Pendulum movement of the heart, which is drawn over to the side affected during inspiration, and away from it during expiration
- d* Frequent coalescence of an area of flatness in the infraclavicular area with the substernal area of cardiac dullness

For a more detailed explanation of these physical signs, the reader is referred to an article that I published on a previous occasion ⁶

I may state here that in a considerable number of cases all these signs as well as the characteristic history are obtainable, in which case the diagnosis is fairly certain. In some cases the picture may not be complete, in which case a roentgen film, or better still, fluoroscopy, may elicit all the physical signs.

The reason for the absence of some of the characteristic features that are usually present in this condition becomes clear when one thinks of the evolution of its physiopathology, that is, the high diaphragm that is frequently found and the paradoxical respiration are due to the paralysis of the adjoining phrenic nerve. In the early stage of carcinoma of the bronchus or even in later stages, if the mass first develops quite distally to the root and hence away from the phrenic nerve, there may be no paralysis and hence no high diaphragm or paradoxical respiration.

The following is an account of 6 cases diagnosed consecutively in my service in the ward during a period of one year. As stated, 2 of these cases were diagnosed by the intern by applying himself to my method. Two of these cases were verified by autopsy findings. In 3 cases bronchoscopy was performed, and in 2, biopsy material showed carcinoma.

REPORT OF CASES

CASE 1—M S, a white man, aged 51, a carpenter, gave an essentially negative family history. He had never complained of a pulmonary difficulty up to three years prior to his admission to the hospital, when he first began to be troubled by a slight cough. This, however, did not prevent him from attending to his work. Three months before admission his cough became very annoying, and he experienced severe pain in the chest. Since then he could not work and had lost 25 pounds (11.3 Kg). He was sent to the hospital by his family physician with the diagnosis of pulmonary tuberculosis.

The age and negative pulmonary history up to the present complaint immediately suggested the possibility of a pulmonary malignant condition. Physical examination revealed the cardiac pendulum phenomenon. The diaphragm, however, was not of the high standing type. Infraclavicular dullness was fused with retrosternal cardiac dullness. A diagnosis of carcinoma of the lung was made. Fluoroscopy revealed a dense shadow in the upper lobe of the left lung. After the patient's first week in the hospital, the cough became very severe and profusely

productive. Physical signs of a cavity soon became apparent. This cavity grew rapidly larger. His expectoration became more profuse and foul. The patient died following a very severe pulmonary hemorrhage. Autopsy revealed a cavity the size of a fist lined by a very ragged, degenerated wall external to which was a grayish-white shell of cartilaginous consistency typical of carcinoma.

CASE 2—I W., a white man, aged 70, had an essentially unimportant family history. He could not reveal any previous serious illness. Eight days prior to his call at the office, he was suddenly taken with an attack of dyspnea, which continued practically without interruption. There was also a sensation of unbearable retrosternal pressure. The family physician diagnosed the condition as a severe paroxysm of asthma.



Fig 1 (case 1) —Primary carcinoma of the left lung

Examination revealed a mild degree of cyanosis and an expression of extreme alarm. There was an area of flatness in the right interscapular space. The diaphragm on that side was not high, and no paradoxical respiration was made out. The blood pressure was 200 systolic and 110 diastolic. An electrocardiogram, however, failed to reveal any evidence of myocardial changes or anything suggestive of a coronary lesion.

A tentative diagnosis of a neoplasm, either mediastinal or pulmonary, was made on the basis of the previous negative pulmonary history, the interscapular flatness and the intensity of the symptoms.

An x-ray film was very suggestive of a tumor beginning at the bifurcation of the larger right bronchus. The subsequent pain necessitated the constant administration of moderate doses of opiates.

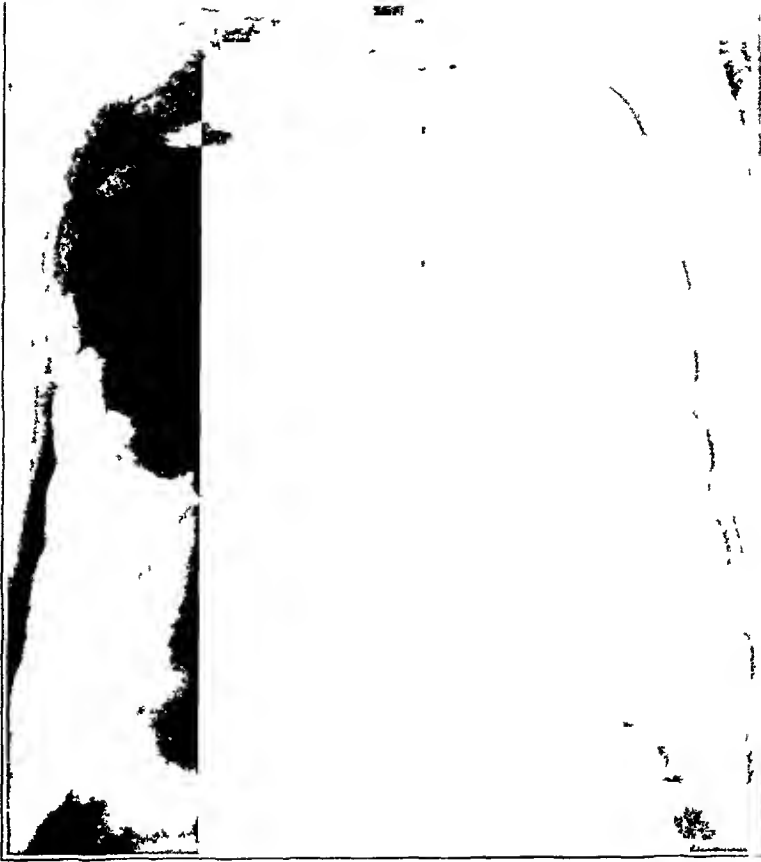


Fig 2 (case 1) —Small cavity, with the fluid level definitely visible in the upper part of the shadow

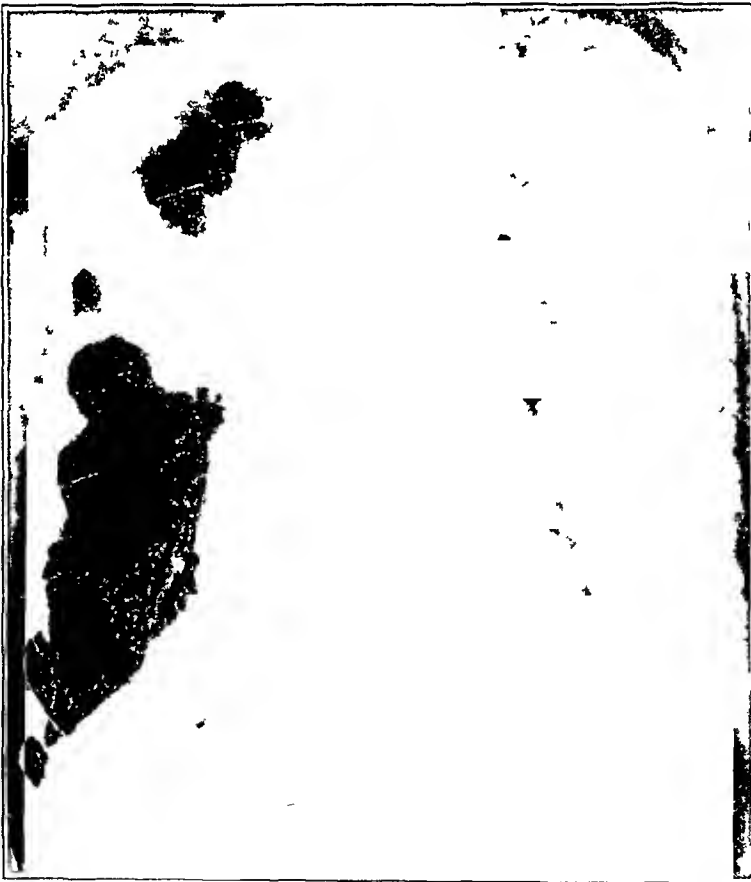


Fig 3 (case 1) —Very large cavity, irregular masses projecting into it are definitely discernible. It is interesting to observe that, while the cancer cavity in its early stage looks very much like an ordinary abscess with its usual fluid level, as it grows larger the cancerous characteristics become evident. The wall is irregular and is studded with irregular masses.

Examination three weeks later revealed a very high diaphragm on the affected side. No fluid was made out. Paradoxical respiration and a resultant seesaw movement of the diaphragm were elicited. A pendulum movement of the heart was questionable by the percussion method, but was clearly made out by the aid of the fluoroscope. A definite diagnosis was then made of primary bronchial carcinoma of the lung.

The dyspnea continued. The pain, however, abated somewhat. The patient died within six weeks after the first examination in a state of extreme dyspnea and exhaustion. No autopsy was performed, but biopsy material obtained by the bronchoscope revealed carcinoma in the lower part of the right bronchus.

CASE 3—R. D., a white man, aged 50, gave an irrelevant family history. There was a previous history of pneumonia one and one-half years before examination, up to which time he had never been sick. He had lost 33 pounds (15 Kg) in



Fig 4 (case 2)—*A*, chest of patient. *B*, chest three weeks later. The diaphragm is high owing to paralysis of the phrenic nerve and a possible collapse of the lower lobe.

the last seven months. He had continued working up to four months before examination, when he began to tire on slight effort. Since then he had also been suffering from dyspnea, which was constant and was not relieved by rest. He applied at that time for medical aid to a very reputable institution. Evidently carcinoma was then suspected, as bronchoscopy was performed at the institution, though with negative results. An axillary gland was also removed at the same institution for biopsy and was found negative for carcinoma. One month later the patient was tapped by his family physician for a pleural effusion. This gave him temporary relief. Shortly afterward dyspnea recurred, and three months after the tap he applied to my service because of his dyspnea and loss of weight.

Physical examination revealed the following. The right side of the chest was flat from the apex to the base, anteriorly as well as posteriorly. Because of the history, a tentative diagnosis of carcinoma of the lungs was made. After aspira-

tion of the fluid, which was serous, the high position of the diaphragm, the paradoxical respiration, the pendulum movement of the heart and fusion of the right upper dull area with the upper sternal cardiac dullness were made out clinically and corroborated by the fluoroscope. The patient presently refused food, became moribund and died from inanition.

At autopsy, a carcinoma involving the upper lobe of the right lung, extending from the right upper bronchus, surrounded by a large area of atelectasis, was found.

CASE 4—B S, a white man, aged 62, gave the following history. Two years before examination he had had a bad cold that confined him to bed for six weeks. The cough had persisted for about one year. A condition then developed



Fig 5 (case 3)—The upper shadow represents carcinoma and atelectasis of the upper lobe of the right lung. The diaphragm is extremely high.

that was diagnosed as asthma. This was shortly followed by a pleural effusion. He had been unable to work since. His chief complaints on admission were pain in the left side of the chest, loss of weight and hemoptysis.

Examination revealed unilateral left exophthalmos. The left pupil was dilated. The left side of the chest was flat on percussion from the apex to the base. After draining a large amount of serous pleural fluid, the characteristic diaphragmatic phenomena and the pendulum movement of the heart could be clearly made out clinically and fluoroscopically. The upward inspiratory excursion of the left side of the diaphragm was very marked. A diagnosis of primary carcinoma of the left lung was made. Bronchoscopy revealed a mass protruding into the lumen below the bifurcation of the left main bronchus. Biopsy was not made.

The patient left the hospital, he died at home from a severe pulmonary hemorrhage.

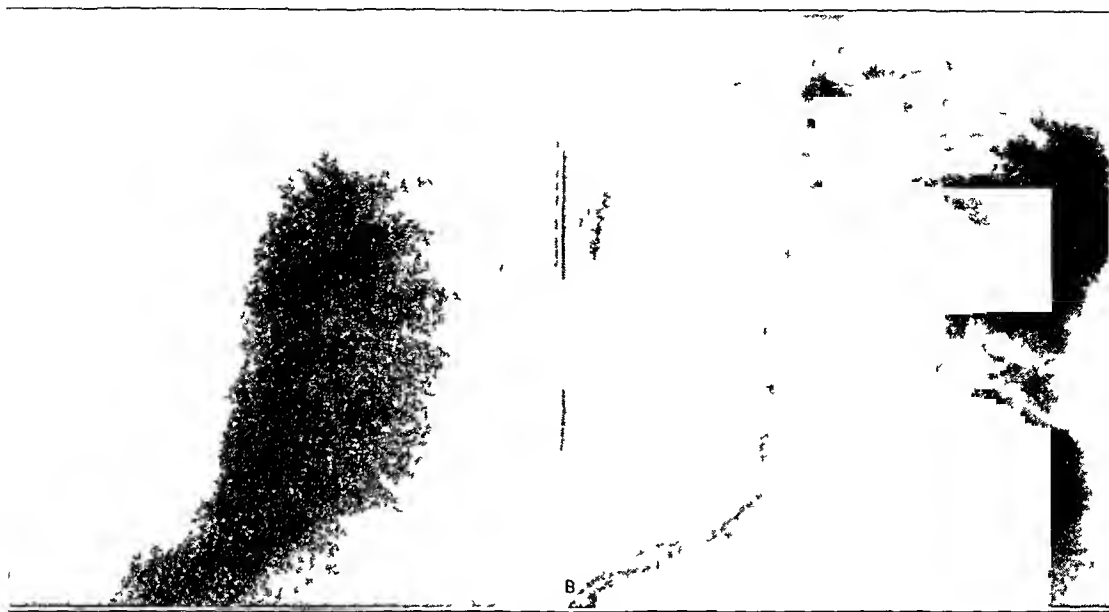


Fig 6 (case 4) —*A*, chest of patient *B*, chest after the pleural fluid had been drained

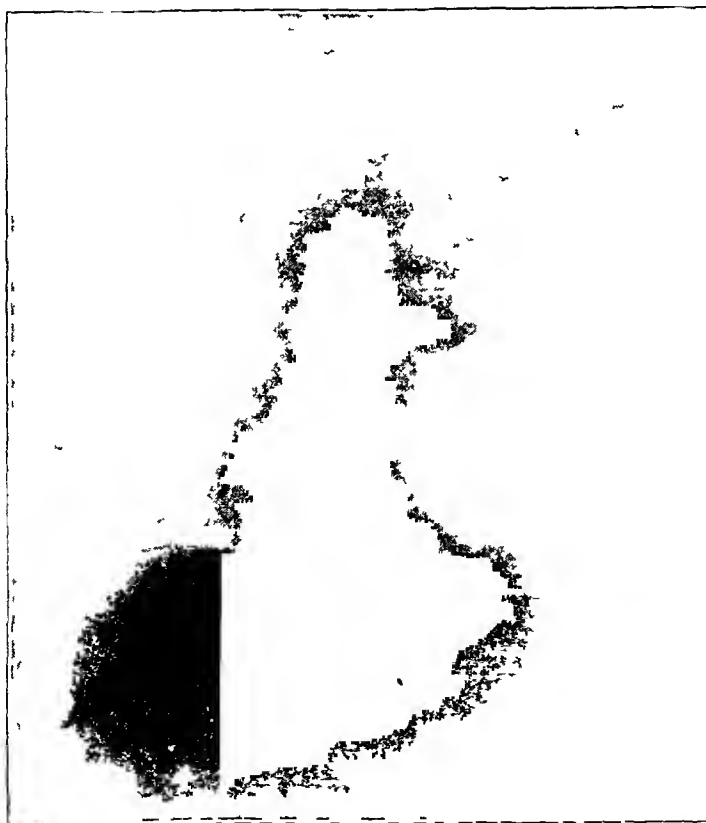


Fig 7 (case 5) —The shadow represents the tumor and the atelectatic lung

CASE 5—B Z, a white man, aged 48, was never sick until a month prior to his admission to the hospital, at which time he started to cough, with a good deal of mucopurulent expectoration which presently became tinged with blood. The patient had pronounced alcoholism. The sputum was repeatedly negative for tubercle bacilli, and the Wassermann reaction of the blood was negative. The patient was sent to the hospital by his family physician with a diagnosis of advanced pulmonary tuberculosis.

Examination revealed a very emaciated person. The upper right side of the chest was extremely flat, chiefly anteriorly. This area of flatness fused with the upper retrosternal cardiac area. A pendulum movement of the heart could be



Fig 8 (case 6) —The growth seems to be located peripherally. There is evidence of upper pulmonary collapse and a high diaphragm.

made out definitely. Diaphragmatic excursion was very limited, but was not paradoxical. A diagnosis of pulmonary carcinoma was made. Bronchoscopy revealed the upper part of the right bronchus partly obstructed by a mass that bled readily. No material was obtained for biopsy. The patient left the hospital and was lost from observation.

CASE 6—Mrs M S, a white woman, aged 60, insisted that she had had a negative pulmonary history up to two years before admission to the hospital, since which time she had been suffering from a mild bronchitis. One year before admission she began to cough severely and experienced intense pain in the right side of the chest. She lost her appetite and weight.

Physical examination revealed extreme flatness over the upper right side of the chest which fused with the upper sternal cardiac dulness. A distinct pendulum movement of the heart, a high diaphragm and paradoxical respiration were clearly made out by percussion and were verified by the fluoroscope. A diagnosis of primary pulmonary carcinoma of the right lung was made. Bronchoscopy was not considered essential. Symptoms of pressure on the superior vena cava—facial swelling and puffiness of the arms—recently developed. The patient was still under observation.



Fig 9 (case 1) —The lung, showing a rugged shell of carcinoma in the upper lobe, with a large irregular cavity

COMMENT

An analysis of the 6 cases shows that pain occurred in 4, effusion in 2, asthmatic symptoms in 2, hemoptysis in 4, a pendulum movement of the heart in all 6, paradoxical respiration in 4, a high diaphragm in 4, fusion of the upper area of flatness with cardiac dulness in 4, cavity formation in 1, pressure on the sympathicus in 1 and terminal pressure on the superior vena cava in 1.

SUMMARY

- 1 Primary pulmonary carcinoma can be diagnosed clinically
- 2 A characteristic history is obtained in the vast majority of cases
- 3 A characteristic complex of physical signs has been described
- 4 The fluoroscope is of great aid in doubtful cases and helps to confirm clinically established ones
- 5 Bronchoscopy and biopsy are rarely necessary to establish a diagnosis

682 High Street

THE USE OF AMIDOPYRINE IN RHEUMATIC FEVER *

MARK P SCHULTZ, M D

NEW YORK

In the treatment of patients with rheumatic fever during the past year in this hospital it has been found that amidopyrine is decidedly superior to other drugs heretofore employed, namely, sodium salicylate, acetylsalicylic acid, the ethyl ester of phenylcinchoninic acid, cinchophen and neocinchophen¹. As an adequate summary of the properties of amidopyrine is not available elsewhere, a brief review of the literature concerning it is presented as a preliminary to an account of the observations presented in this paper on rheumatic fever.

REVIEW OF THE LITERATURE

Filehne,² in 1896 and in 1897, described the synthesis, the properties and a few preliminary therapeutic trials of an antipyretic and analgesic which he arbitrarily named "pyramidon," but which he designated more accurately as 4-di-methyl amino-antipyrine. Antipyrine, a condensation product of methyl-phenyl hydrazine and aceto-acetic ester, was first converted by Stolz,³ in 1893, into amidopyrine, or pyramidon, by substituting a di-methyl group in the fourth position⁴. Isomeric forms of the compound have been described⁵.

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* From the Hospital of the Rockefeller Institute for Medical Research

1 Boots, R H, and Miller, C P. A Study of Neocinchophen in the Treatment of Rheumatic Fever, *J A M A* **82** 1928 (March 29) 1924. Miller, C P, and Boots, R H. The Treatment of Rheumatic Fever with the Ethyl Ester of Phenylcinchoninic Acid, *J Lab & Clin Med* **10** 34, 1924. Swift, Homer F. The Treatment of Rheumatic Fever, Boston *M & S J* **187** 331, 1922.

2 Filehne, W. Ueber das Pyramidon, ein Antipyrinderivat, *Berl klin Wchnschr* **33** 1061, 1896, *Das Pyramidon*, *Ztschr f klin Med* **32** 569, 1897.

3 Klatt, H. Ueber das Pyramidon, *Aerztl Rundschau* **15** 545, 1905.

4 Fournau, Ernest. Preparation des medicaments organiques, Paris, J B Baillière et fils, 1922. Frankel, S. Die Arzneimittel-Synthese auf Grundlage der Beziehungen zwischen chemischem Aufbau und Wirkung, ed 2, Berlin, Julius Springer, 1906. Francis, Francis E, and Fortesque-Brickdale, J M. The Chemical Basis of Pharmacology, London, 1908, p 206.

5 Kobert, R. Beitrage zur Kenntnis einiger Pyrazolonderivate, *Ztschr f klin Med* **62** 57, 1907.

The chemical and physical properties have been studied in some detail,⁶ and many color reactions have been devised for identification.⁷ Amidopyrine is a yellow-white, almost tasteless, crystalline powder, readily soluble in water (1:10) and faintly alkaline in solution. The compound is very susceptible to the action of oxydases, and for this reason certain pharmacologic combinations are contraindicated.⁸

The drug is rapidly absorbed and excreted. After moderate doses by mouth, it appears in the blood and urine within twenty minutes,² the urine remains free from detectable traces after two hours. The rapidity of excretion is also demonstrated by the fact that 300 per cent of the intravenous fatal dose may be given to cats by the administration of fractions of the total quantity over a period of twenty-four hours.⁹ Although readily decomposed in the body, for only 1 per cent appears unchanged in the urine, the site of destruction has not been identified.¹⁰ The compound is eliminated in the urine chiefly as uramino-antipyrine, in combination with glycuronic acid, and in certain persons as an unidentified complex derivative which readily oxidizes to rubizonic acid, thereby imparting a pink color to the urine.¹¹ Apert¹² observed such urinary color change, usually beginning four hours after a dose

6 Filehne (footnote 2, first reference) Cushny, Arthur R. A Text-Book of Pharmacology and Therapeutics, ed 7, Philadelphia, Lea & Febiger, 1918, p 473. Meyer, H. H., and Gottlieb, R. Experimentelle Pharmakologie als Grundlage der Arzneibehandlung, ed 5, Berlin, Urban & Schwarzenberg, 1921, p 542.

7 Barral, E. Nouvelles réactions colorées du pyramidon, Bull. Soc. méd. d'hôp. de Lyon **2**:206, 1903. Hoffmann, Paul. Vergleichende Reaktionen von Antipyrin, Pyramidon und Verwandten und Schicksal des Pyramidon im Tierkörper, Arch. internat. de pharmacodyn. et de therapie **6**:171, 1899. Jolles, Adolf. Ueber den Nachweis des Pyramidons (Dimethylamido-antipyrins) im Harn, Ztschr. f. anal. Chem. **37**:441, 1898.

8 Bondouy, T. Action du ferment oxydant de la gomme arabique sur le pyramidon, Trav. scient. Univ. de Rennes **2**:281, 1903. von Waldheim, M. Ursache und Verhütung der Inkompatibilität des Pyramidons und des Gummis, Ztschr. d. allg. österr. Apoth.-Ver. **56**:1025, 1902.

9 Koppányi, T., and Lieberman, A. Studies on the Duration of Action of Drugs. I. Analgesics and Hypnotics, J. Pharmacol. & Exper. Therap. **39**:177, 1930.

10 Hoffmann (footnote 7, second reference) Oswald, Adolf. Chemische Konstitution und pharmakologische Wirkung, Berlin, Borntraeger, 1924. Jaffe, M. Ueber das chemische Verhalten des Pyramidons im Organismus, Internat. Beitr. z. inn. Med. (Leyden), Berl. **2**:1, 1902.

11 Francis, Francis E., and Fortesque-Brickdale (footnote 4, third reference), Hoffmann (footnote 7, second reference) Jolles (footnote 7, third reference) Gregor, K. Ueber einen bei innerlicher Anwendung von Pyramidon im Harn. Die Behandlung des Unterleibstypus mit Pyramidon, Munchen med. Wchnschr. **54**:566, 1907. Remmets. Einiges über Pyramidon, Prakt. Arzt **42**:265, 1902.

12 Apert, E. Les urines rouges dans la médication par le pyramidon, Arch. auftretenden roten Farbstoff, Therap. Monatschr. **14**:298, 1900. Leick, Bruno. gen. de méd. **2**:1665, 1904.

of 1 Gm, as a peculiar response in about one third of his patients who were receiving therapeutic doses, although no correlation was established with any other unusual reaction to the drug

The mechanism of antipyresis has not been studied in much detail. There is great increase in heat loss as measured in the calorimeter¹³. This is occasioned by peripheral vasodilatation and increased perspiration, thought to be due to a central action of the drug. It occurs after small doses in febrile, and after large doses in normal, animals. Although heat production is slightly decreased,¹⁴ tissue oxidation is depressed less than in the instance of other antipyretics.¹⁵ Therapeutic doses have a very slight effect on the temperature of normal man,¹⁶ but large doses frequently have been observed to reduce the temperature in afebrile animals.¹⁷

The analgesic effect is thought to reside in a direct action on the thalamus.¹⁸

In the earlier French literature, one frequently encounters the statement that amidopyrine generally accelerates metabolism, because a relatively increased excretion of urinary nitrogen as urea was observed during medication.¹⁹ This conclusion seems questionable on such slender evidence, although it is possible that the results quoted may have been associated with altered kidney excretory function similar to that demonstrated more recently in the instance of other antipyretics.²⁰ Inconclusive studies have been made of the effect of the drug on oxygen

13 Filehne (footnote 2, second reference) Gessler, H. Ueber den Einfluss des Pyramidons auf den Stoffwechsel, *Arch f exper Path u Pharmacol* **98** 257, 1923

14 Gessler (footnote 13, second reference)

15 Nitzescu, I. I., and Cosma, I. L'action de quelques antipyrétiques sur la respiration des tissus, *Compt rend Soc de biol* **89** 1406, 1923

16 Filehne (footnote 2, second reference) Blanc, A. Étude thérapeutique sur le pyramidon, *These de Paris*, 1903. Hollo, Julius. Die Beeinflussbarkeit subfebriler Temperaturen durch Pyramidon, *Wien klin Wchnschr* **42** 369, 1929

17 Filehne (footnote 2, second reference) Klatt (footnote 3) Lepine, R. Sur la valeur clinique du pyramidon, *Lyon med* **85** 215, 1897

18 Hoff, H., and Wermer, P. Klinische Untersuchungen über den Angriffspunkt der Analgetica, *Klin Wchnschr* **8** 488, 1929

19 Blanc (footnote 16, second reference) Bertherand, L. Contribution à l'étude du pyramidon et de ses sels, *Bull gen de therap* **141** 243, 1901, **142** 276, 1901. Bardet, G. Action antithermique du pyramidon, *Bull gen de therap* **141** 367, 1901. Robin, Albert, and Bardet, G. Un médicament aromatique, analgesique, et antipyrétique excitateur des échanges organiques, le diméthyl-amido-antipyrine ou pyramidon, *Compt rend Cong internat de med, Paris*, 1900 (Sect therap), p 137

20 Myers, V. C., and Kilian, J. A. Studies on the Influence of Phenylcinchoninic Acid and the Ethyl Ester of Paramethylphenyl-Cinchoninic Acid on Renal Excretion, *J Pharmacol & Exper Therap* **18** 213, 1921

consumption and internal respiration²¹ Retention of water and sodium chloride, possibly the result of a central action, have been observed in animals²²

There is definite effect on sugar metabolism, in that therapeutic doses lower the blood sugar level slightly in normal men and animals,²³ but increase it in persons with severe diabetes and in depancreatectomized dogs²⁴ Very large, toxic doses in animals uniformly cause an increase in the blood sugar²⁵ These observations are interpreted as indicating a direct action on the pancreas Temporarily increased excretion of sugar in diabetic persons has been observed frequently coincident with the administration of amidopyrine²⁶

The general symptoms following varied doses by different routes of administration have been studied extensively in several species of animals²⁷ In the dog, 0.2 Gm per kilogram of body weight by mouth is the usual maximum sublethal dose, and on the basis of comparative weights roughly corresponds with from 8 to 10 Gm in man²⁸

Miscellaneous studies of the effects of the drug have demonstrated the following (1) a peripheral action in lowering the tonus of smooth muscle,²⁹ (2) a depression of the higher centers (an observation of the behavior of rats in a circular maze³⁰), (3) a slight elevation of the

21 Robin and Bardet (footnote 19, fourth reference)

22 Gessler (footnote 13, second reference) Averbuck, S H Ueber die Diureschemmung durch Antipyretika, Arch f exper Path u Pharmacol **157**:330, 1930

23 Gessler (footnote 13, second reference) de Carvalho, Alberto Contribution à l'étude de l'action des antipyrétiques sur la glycémie, Compt rend Soc de biol **98** 1583, 1928

24 Chiari, H, and Regler, R Zur Frage der Beziehung zwischen Warme-Regulation und Zuckerstoffwechsel Die Beeinflussung des Blutzuckers durch Fiebermittel der Pyrazolengruppe, Ztschr f d ges exper Med **46**:443, 1925

25 Legendre, Charles Sur le pyramidon Étude expérimentale et thérapeutique, Paris, 1897, thèse no 270 Lépine, R Sur le pyramidon, Rev de med, Paris **17** 196, 1897

26 Bertherand (footnote 19, second reference) Robin and Bardet (footnote 19, fourth reference) Henneberg, H Eine Migränvergiftung, Therap Monatsh **18** 50, 1904

27 Filehne (footnote 2, second reference) Blanc (footnote 16, second reference) Lépine (footnote 17, third reference and footnote 25, second reference)

28 Lépine (footnote 17, third reference)

29 Januschke, H, and Lasch, F Ueber die periphere Wirkung des Pyramidons I Mitteilung Die Wirkung des Pyramidons auf die glatte Muskulatur, Arch f exper Path u Pharmacol **114**:70, 1926, Ueber die Wirkung des Pyramidons auf die Muskulatur des Darmes, Klin Wchnschr **5**:321, 1926 Lasch, F, and Perutz, A Pharmakologische Untersuchungen über die Wirkung des Pyramidons auf das Genitale, Arch f Dermat u Syph **150**:474, 1926

30 Macht, D I, and Bloom, W Effect of Some Antipyretics on the Behavior of Rats in the Circular Maze, J Pharmacol & Exper Therap **17** 21, 1921

threshold of hearing in man,³¹ (4) no effect on muscular coordination,³² and (5) a capacity of inducing hypersensitiveness in animals which may be passively transferred³³ With regard to properties that might impair therapeutic value, amidopyrine proved inferior to the other antipyretics and analgesics with which it was compared in these experiments only in the depression of higher cerebral function

After the introduction of amidopyrine by Filehne in 1896, it was given many clinical trials in a wide variety of diseases, and was most extensively used in typhoid fever³⁴

There were diverse opinions regarding the value of the drug in this disease, but the composite conservative conclusion seems to have been that in instances in which baths are inadvisable by reason of extreme delirium or objection on the part of the patient, and in the presence of great weakness, perforation or bleeding, it may be of use Amidopyrine in rather small doses (from 0.15 to 0.3 Gm) frequently repeated was effective as an antipyretic and in clearing the sensorium, but there was occasional vomiting, thought by some observers to be due to the medication With the disappearance of fever, symptoms of collapse, with weak pulse, profound drop in temperature and cyanosis, some-

31 Macht, D I, Greenburg, J, and Isaacs, S The Effect of Some Antipyretics on the Acuity of Hearing, *J Pharmacol & Exper Therap* **15** 149, 1920

32 Macht, D I, Isaacs, S, and Greenberg, J P On the Influence of Some Antipyretics on the Neuro-Muscular Co-Ordination Test of "Tapping," *Proc Soc Exper Biol & Med* **15** 61, 1918

33 Biberstein, H Beitrage zur passiven Uebertragung der Ueberempfindlichkeit gegen chemisch bekannte Stoffe, *Ztschr f Immunitatsforsch u exper Therap* **48** 297, 1926

34 Filehne (footnote 2, first reference) Klatt (footnote 3) Leick (footnote 11, fifth reference) Blanc (footnote 16, second reference) Lepine (footnote 17, third reference) Brandies, A Ueber die Behandlung des Typhus abdominalis mit Pyramidon, *Prag med Wchnschr* **22** 525, 1897 Butters Ueber Pyramidon, *Festschr z Eroffn d n Krankenh d Stadt Nurnb*, 1898, p 505 Byk, L Ueber die Anwendung des Pyramidons bei Typhus abdominalis, *Deutsche med Wchnschr* **29** 51, 1903 Gerest and Rigot Traitement de la fièvre typhoïde par le pyramidon, *Loire med* **19** 281, 1900 Hirtz L'observation de plusieurs malades ayant eu une chute brusque de température après l'injection de doses légères de pyramidon, *Bull et mem Soc med d hôp de Paris* **33** 959, 1912 À propos de l'emploi du pyramidon chez les typhiques, *Presse med* **54** 573, 1912 Hodlmoser, C Ueber den Wert des Pyramidons für die Behandlung des Abdominaltyphus, *Wien klin Wchnschr* **18** 103, 1905 Horneffer, Curt Pyramidon (Dimethylamidoantipyrin), *Berl klin Wchnschr* **34** 759, 1897 John, M Zur Pyramidonbehandlung des Typhus, *Munchen med Wchnschr* **59** 987, 1912 von Krannhals, H Ueber die Anwendung des Pyramidon beim Abdominaltyphus, *Munchen med Wchnschr* **51** 2175, 1904 Philibert, A Les perforations intestinales au cours de la fièvre typhoïde, *Gaz d hôp* **83** 237, 1910 Valentini Ueber die systematische antifebrile Behandlung des Unterleibstyphus mit Pyramidon, *Deutsche med Wchnschr* **29** 273, 1903

times occurred. As no other untoward effects of the medication were encountered, the conclusion was reached by some observers that these symptoms were not in the nature of a side action, but rather the direct result of inadvisable lowering of the temperature. In particular, the duration of the febrile phase of the disease and the development of myocarditis were uninfluenced.³⁵ The ability of the patient to elaborate specific agglutinins was not depressed.³⁶

Amidopyrine has also been used in febrile tuberculosis of all forms.³⁷ Often a complete antipyretic effect was secured, if not, other antipyretics likewise were ineffective. Except for excessive sweating, no untoward reactions were observed in most instances, while appetite was occasionally increased and malaise overcome to a degree apparently beneficial. However, the natural progress of the disease was uninfluenced.

Patients with a variety of febrile diseases, including pneumonia,³⁸ influenza,³⁹ bronchitis,⁴⁰ erysipelas,⁴¹ scarlet fever,⁴² puerperal sepsis,⁴³

35 Widenmann, A. *Pyramidonbehandlung des Unterleibstypus*, *Med. Klin.* **2** 814, 1906. Remberg, Pierre. *Traitement de la fièvre typhoïde par le pyramidon*, *Nouv. remèdes* **19** 438, 1903.

36 Bemisch, M. *Ueber den Einfluss der Antipyrese auf die Agglutinationskraft des Blutes beim Abdominaltyphus*, *Ztschr. f. klin. Med.* **45** 51, 1902.

37 Filehne (footnote 2, first reference). Klatt (footnote 3). Blanc (footnote 16, second reference). Bertherand (footnote 19, second reference). Robin and Bardet (footnote 19, fourth reference). Butters (footnote 34, seventh reference). Gerest and Rigot (footnote 34, ninth reference). Horneffer (footnote 34, thirteenth reference). Kétly, L. *Pyramidon*, *Heilkunde* **4** 12, 1899. Blumenthal, A. *Therapeutische Verwendung von Pyramidon und seinen Salzen bei Phthisis pulmonum*, *Deutsche Aerzte-Ztg.*, 1901, no. 19, p. 438. Hirschcron, J. *Neuere Erfahrungen mit Pyramidon*, *Allg. Wien. med. Ztg.* **46** 142, 1901. Kobert, R. *Pharmakotherapeutische Ruckblicke. II. Die Antipyretica*, *Deutsche Aerzte-Ztg.*, 1899, no. 2, p. 30. Lublinsky, W. *Ueber die Wirksamkeit des Pyramidons bei dem Fieber der Phthisiker*, *Therap. Monatsh.* **15** 513, 1901. Muller. *Ueber Pyramidon*, *Deutsche Prax.* **12** 680, 1903. Pollak, J. *Einige neue Medicamente in der Phthiseotherapie*, *Wien. klin. Wchnschr.* **13** 59, 1900. Tauszk, F. *Die Salze des Pyramidons*, *Deutsche Prax.* **14** 204, 1905. Roth, D. *Ueber Wirkungsweise des Pyramidons bei verschiedenen Krankheitszustanden*, *Wien. klin. Wchnschr.* **10** 964, 1897.

38 Filehne (footnote 2, first reference). Butters (footnote 34, seventh reference). Horneffer (footnote 34, thirteenth reference). Hirschcron (footnote 37, tenth reference). Muller (footnote 37, fourteenth reference).

39 Blanc (footnote 16, second reference). Horneffer (footnote 34, thirteenth reference). Muller (footnote 37, fourteenth reference).

40 Hirschcron (footnote 37, eleventh reference). Muller (footnote 37, fourteenth reference).

41 Filehne (footnote 2, first reference). Blanc (footnote 16, second reference). Butters (footnote 34, seventh reference). Horneffer (footnote 34, thirteenth reference).

42 Filehne (footnote 2, first reference). Horneffer (footnote 34, thirteenth reference).

43 Muller (footnote 37, fourteenth reference).

meningitis,⁴⁴ mumps,⁴⁵ smallpox,⁴⁵ measles⁴⁴ and malaria,⁴⁶ have been treated with amidopyrine, with effective antipyresis in all except malaria.

In 1903, Muller⁴³ reported beneficial effects in a number of cases of measles, and more recently,⁴⁷ striking abortive and apparently curative properties brought about in this disease by amidopyrine have been observed, although not universally.⁴⁸

Because the antipyretic effects of amidopyrine have been so impressive, it has been proposed on the basis of extensive clinical studies of patients treated for tuberculosis that a temperature not lowered by moderate doses is, in fact, a normal temperature.⁴⁹ Interesting effects were observed by Weltmann,⁵⁰ who gave single doses of 1 Gm to patients with subfebrile temperatures following a variety of long and severe infections. In some cases there was only a temporary return of the temperature to normal, indicating a persisting infection, in others the temperature became normal and remained there. Weltmann suggested that in the latter instances the regulating center may have been "set at a higher level" as a result of the long-continued febrile state.

There are occasional, scattered references to a sedative action of amidopyrine. It is probably this property, in addition to a possible influence of therapeutic doses in relaxing smooth muscle, that accounts for a reported beneficial effect in asthma.⁵¹

Striking examples of the analgesic potency of amidopyrine are reported in the literature.⁵² In migraine, tic douloureux, tabetic crises

44 Butters (footnote 34, seventh reference)

45 Blanc (footnote 16, second reference)

46 Roth (footnote 37, seventeenth reference)

47 Loewenthal, Max. Amidopyrin in the Treatment of Measles, *Brit M J* **2** 51, 1924. Collier, J. I. Treatment of Measles with Amidopyrin, *ibid* **1** 1093, 1930. Ronaldson, G. W., and Collier, J. I. Amidopyrin in the Treatment of Measles, *ibid* **2** 994, 1930.

48 Attlee, W. H. W. Amidopyrin in the Treatment of Measles, *Brit M J* **2** 996, 1930.

49 Hollo (footnote 16, third reference), Ueber eine neue Methode zur Beurteilung subfebriler Temperaturkurven im Verlaufe der Lungentuberkulose, *Beitr z Klin d Tuberk* **36** 29, 1916. Mayrhofer, Heinrich. Die Beeinflussbarkeit subfebriler Temperaturen durch Pyramidon, *Wien klin Wchnschr* **42** 107, 1929.

50 Weltmann, O. Ueber den Einfluss einer einmaligen massiven Pyramidon-Dosis auf postinfektiöse Temperatursteigerungen (Pyramidonstoss), *Med Klin* **25** 1659, 1929.

51 Albrecht. Ueber Pyramidon, besonders beim Asthma, *Therap d Gegenw* **4** 476, 1902.

52 Blanc (footnote 16, second reference). Bertherand (footnote 19, second reference). Robin and Bardet (footnote 19, fourth reference). Hirschcron (footnote 37, eleventh reference). Muller (footnote 47, fourteenth reference). Althausen. Schmerzstillende Wirkung des Pyramidons, *Med Klin* **10** 1498, 1914. Laudenheimer, Rudolf. Ueber Anwendung des Pyramidons bei Nervenkrankheiten, *Therap Monatschr* **12** 177, 1898. von Donat. Pyramidon in der Zahnheilkunde, *Deutsche zahnarztl Wchnschr* **10** 436, 1907.

and other painful diseases, it has often been found effective when other similar drugs have failed, at times even when opiates were insufficient⁵³

The first use of this drug in rheumatic fever was reported by Roth, in 1897⁴⁶ He favored it especially, because there were no undesirable incidental effects, and he was so deeply impressed by the powerful antisymptomatic properties that he proposed a theory of specific action in this disease During the few succeeding years (from 1897 to 1903), similar observations were continued by Breyer,⁵⁴ Robin and Bardet, Pauli,⁵⁵ Hirschkron, Bertherand and Muller All except Bertherand, who reported two failures, confirmed Roth's observations, and considered amidopyrine the drug of choice in the treatment for this disease

As chemically induced antipyresis generally fell into disfavor, the striking advantages of amidopyrine in the treatment for rheumatic fever seemed to be forgotten The value of the drug in this connection was accidentally rediscovered by Schottmuller,⁵⁶ who reported briefly in 1927, and in more detail in 1929 His assistant, Bodensstab,⁵⁷ also reviewed the subject in 1928 They found that therapeutic doses can be given without provoking symptoms of toxicity, and that very few cases are refractory Instances were cited in which amidopyrine afforded complete relief when symptoms of intoxication enforced discontinuance of sodium salicylate, and when the latter, although tolerated in the usual therapeutic doses, was ineffective After sodium salicylate had been used almost exclusively for thirty years in the treatment for rheumatic fever in the clinic of Professor Schottmuller, a change was made to amidopyrine One other recent reference to the value of the drug in rheumatic fever was made by Motzfeldt⁵⁸

The levels of therapeutic and toxic doses and the relation of the size of the dose to the appearance of untoward effects can be estimated very well from the experiences in the various diseases mentioned

53 Lépine (footnote 17, third reference) Kohn, S *Pyramidon und Morphinum*, Prag med Wchnschr **32** 222, 1907

54 Breyer, A *Die praktische Verwerthbarkeit des Pyramidons als fieberwiedrigen und schmerzstillenden Mittels*, Inaug Dissert, Breslau, 1899

55 Pauli, W *Ueber Nebenwirkungen des Pyramidons*, Centralbl f d ges Therap **18** 129, 1900

56 Schottmuller, H *Therapeutische Erfahrungen IV Behandlung des akuten und chronischen Gelenkrheumatismus mit Pyramidon*, Munchen med Wchnschr **74**:861, 1927, *Ueber akute Gelenkentzündungen, ihre Aetiologie und Behandlung*, *ibid* **76** 499, 1929

57 Bodensstab, Rudolf *Ueber die Behandlung der Polyarthritidis rheumatica acuta und chronica mit Pyramidon*, Deutsches Arch f klin Med **159**:171, 1928

58 Motzfeldt, K *Salicylates in the Treatment of Rheumatic Fever*, Acta med Scandinav, 1930, supp 34, p 8

The especial instance of typhoid fever, in which symptoms of circulatory collapse sometimes accompany antipyresis, has been discussed in this connection. In the treatment for tuberculosis, the doses were usually small, but from 1 to 2 Gm was sometimes given daily for months. In miscellaneous febrile diseases similar amounts were effective, but were not continued for long periods. As an analgesic for various pains of nerve origin, small quantities were often sufficient, however, single doses of 1.25 Gm⁵⁹ and daily doses of from 2 to 3 Gm were given⁶⁰. In rheumatic fever, the earlier observers employed from 1 to 2 Gm, rarely 3 Gm, daily. Muller at one time raised the quantity to 10 Gm, and continued the administration at a level of from 4 to 6 Gm daily for three months. Schottmuller found that the instances were rare, indeed, in which more than 3 Gm was required daily, and considered this the maximum therapeutic dose. He found, however, that full therapeutic doses may be continued for months without harm.

Several authors called attention to the remarkable constancy of response in different persons, the absence of habit formation and the fact that there is no increase in tolerance or cumulative effect from long-continued administration⁶¹. Apert¹² observed that children are tolerant to very large quantities, but other authors recommended smaller doses for them. Loewenthal⁶² gave the formula he used with reference to age.

Many observers, regardless of the size of dose used or the disease for which the patient was treated, reported an entire absence of important untoward effects⁶³. Others encountered instances of idiosyncrasy or of undesirable incidental reactions in some patients after large doses. As has been noted, symptoms of collapse occasionally followed the use of the drug in typhoid fever. They have been observed in other patients twice by Neisser⁶⁴ (in one instance after a dose of 0.2 Gm), occasionally by Mesnard⁶⁵ in persons with alcoholic delirium or depres-

59 Laudenheimer (footnote 52, seventh reference)

60 Robin and Bardet (footnote 19, fourth reference) Legendre (footnote 25, first reference)

61 Filehne (footnote 2, first reference) Remmets (footnote 11, sixth reference) Horneffer (footnote 34, thirteenth reference) Althausen (footnote 52, sixth reference) Kohn (footnote 53, second reference)

62 Loewenthal (footnote 47, first reference)

63 Klatt (footnote 3) Leick (footnote 11, fifth reference) Remmets (footnote 11, sixth reference) Butters (footnote 34, seventh reference) Gerest and Rigot (footnote 34, ninth reference) Horneffer (footnote 34, thirteenth reference) Valentini (footnote 34, seventeenth reference) Remberg (footnote 35, second reference) Hirschcron (footnote 37, eleventh reference) Pauli (footnote 55)

64 Neisser. *Neuere diagnostische und therapeutische Methoden beim Typhus*, Berl. klin. Wchnschr. **41** 821, 1904

65 Mesnard, P. A. *Emploi thérapeutique du pyramidon*, Presse méd. **2** 762, 1902

sion, and once by Blumenthal ⁶⁶ in a patient severely ill with tuberculosis Henneberg ⁶⁷ described vomiting and dizziness in a diabetic patient Laudenheimer ⁶⁸ reported that as an analgesic in an afebrile patient, a single dose of 0.4 Gm caused a complaint of precordial "anxiety," and that in another person the same complaint followed a dose of 1.25 Gm Schottmuller ⁶⁹ occasionally observed gastric disturbances on continued daily doses of over 3 Gm Pauli ⁵⁵ mentioned one instance of a painful axillary paresthesia after long-continued administration Mild symptoms, such as weakness, fatigue, malaise, loss of appetite and dizziness, have been reported very rarely, usually following large doses of the drug or in patients in whom such developments might be anticipated incident to their disease An extensive bibliography with reference to side actions observed in patients was given by Seifert ⁷⁰

Skin manifestations following amidopyrine have been reported only infrequently Transient purpura, urticaria or erythema have been noted in one or two patients each by three observers ⁷¹ Five more severe reactions ⁷² (progressing to subcutaneous edema and the formation of bullae), some of them due to a proprietary medicine, "midol," ⁷³ containing amidopyrine, have been described in detail A few of these patients were sensitive to several coal-tar derivatives

Attention has also been called to the absence of certain evidences of toxicity that similar coal-tar derivatives may cause in therapeutic doses, there is no deleterious effect on hemoglobin, the normal or diseased kidney is not taxed, and there is no direct depressing effect on the circulation ⁷⁴ The absence of symptoms similar to those of salicylism is universally noted

66 Blumenthal (footnote 37, tenth reference)

67 Henneberg (footnote 26, third reference)

68 Laudenheimer (footnote 52, seventh reference)

69 Schottmuller (footnote 56, second reference)

70 Seifert, Otto Die Nebenwirkungen der modernen Arzneimittel, Kabitzsch, Wurzburg, 1915

71 Bertherand (footnote 19, second reference) Gerest and Rigot (footnote 34, ninth reference) Widenmann (footnote 35, first reference)

72 Hallopeau Sur l'apparition d'exanthèmes identiques après l'ingestion d'antipyrine, d'aspirine et de pyramidon, Bull Soc franç de dermat et syph **17** 242, 1906 Reitter, Carl Exanthem nach Pyramidongebrauch, Munchen med Wchnschr **50** 140, 1903 Zieler Pyramidonexanthem, Arch f Dermat u Syph **86** 311, 1907 Bechet, Paul E Extensive Dermatitis Medicamentosa, Following the Use of Midol (Pyramidon), J A M A **59** 1289 (Oct 5) 1912

73 Editorial "The Propaganda for Reform" Pyramidon Entering the Patent-Medicine Field—Midol, J A M A **59**.461 (Aug 10) 1912

74 Filehne (footnote 2, first reference) Francis and Fortesque-Brickdale (footnote 4, third reference) Leick (footnote 11, fifth reference) Blanc (footnote 16, second reference) Bertherand (footnote 19, second reference) Remberg (footnote 35, second reference) Kobert (footnote 37, twelfth reference) Kohn (footnote 53, second reference)

Five cases of poisoning have been reported. Single toxic doses of 5 Gm⁷⁵ and 7 Gm⁷⁶ have been survived. Death has occurred after the administration of an unknown quantity,⁷⁷ and in two instances half an hour following doses of 30 Gm taken by mistake⁷⁸. The autopsy observations were negative in each case. A fall in temperature, vomiting, a sense of suffocation and precordial pain, cold sweats, chills, weak and irregular pulse, depressed reflexes and cyanosis, followed by delirium, convulsions and coma, were the usual findings.

EFFECTS OF AMIDOPYRINE OBSERVED IN RHEUMATIC FEVER

All the drugs used in rheumatic fever are effective, probably through purely antisymptomatic properties⁶⁸. They are analgesics, antipyretics and antiphlogistics. With this in mind, a plan of treatment about to be described has been evolved in the hospital of the Rockefeller Institute for Medical Research. The use of one of these agents is indicated in any of the following circumstances: (1) pain or discomfort arising from arthritis, pericarditis or pleurisy, (2) exhausting fever, and (3) extreme "toxicity". The dose is increased until a therapeutic result is secured, the only limitation being evidences of intoxication from the drug. Then, an effort is made to maintain, as it were, a balance between the effects of the disease and the counter-effects of the medication. In other words, after the requisite daily dose is determined, it is lowered slightly from time to time, particularly on any evidence that the disease is less active, in order that the dose may be kept at the lowest level effective. An example of this is demonstrated in chart 1. In the case illustrated in the chart the dose was gradually reduced beginning on May 27, and the drug was discontinued on June 5. There was immediate relapse. A second withdrawal seemed indicated on June 24, but after a slight reduction from the previous level, symptoms reappeared (The temperature elevation, from July 20 to 25, which was not abated by increased doses of amidopyrine, was thought to be due to the effect of hot weather on a patient with inadequate blood circulation. During the interval indicated, the temperature in this patient's room occasionally rose to 110 F. There were no signs that could be interpreted as indicating a more active infection. Subjectively, there was improvement. A distinct loss in weight is to be noted on the chart.) On a third trial, beginning on September 27, the drug was withdrawn entirely for a few days. It was again required, but for the succeeding two months, 0.6 Gm daily.

75 Dandrieu, P. Empoisonnement par le pyramidon, guérison, *Province méd.*, Paris **24** 532, 1913.

76 Rotky, H. Pyramidonvergiftung, *Wien Arch f inn Med* **10** 595, 1925.

77 Geill, Torben. Ein Fall von todlicher Vergiftung durch Pyramidon, *Deutsche Ztschr f d ges gerichtl Med* **7** 344, 1926.

78 Prouzerque, Remy. Note sur la diffusion et la localisation du pyramidon, *J de pharm et chim* **27** 372, 1923.

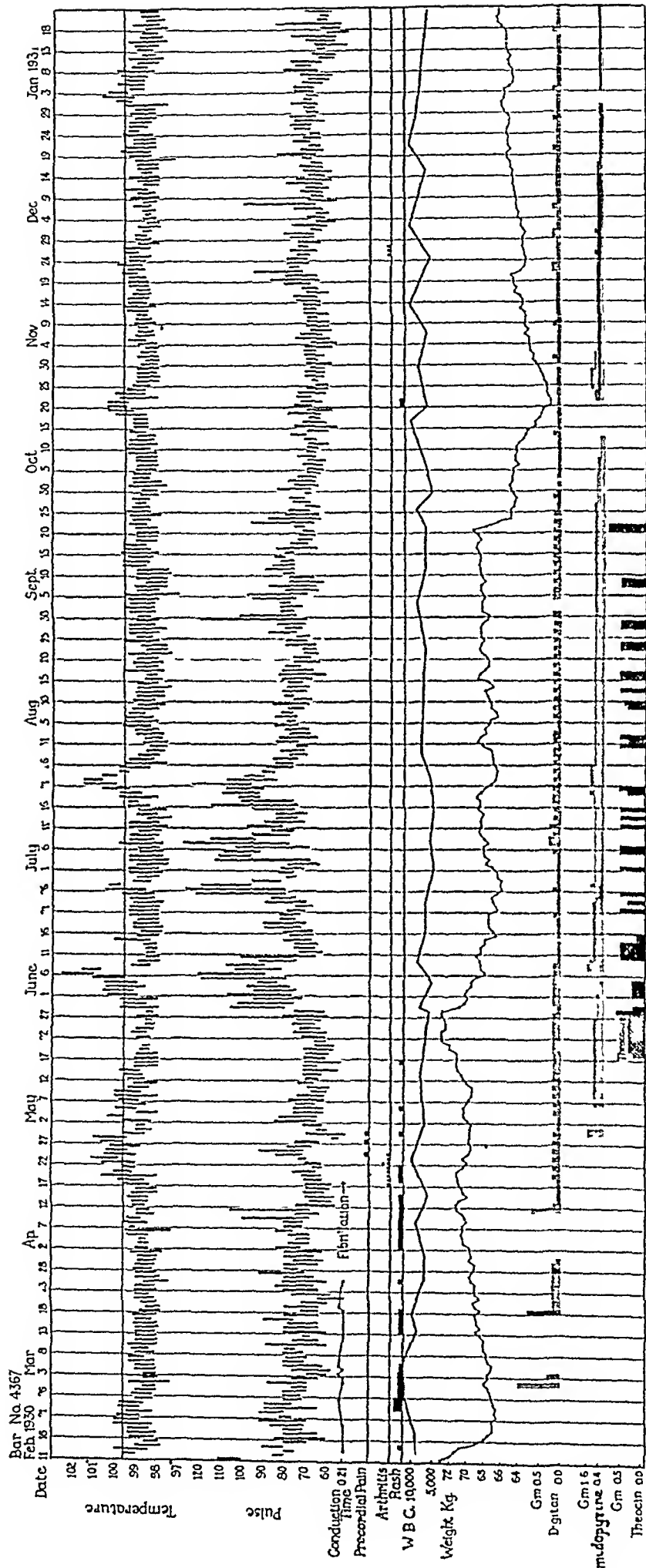


Chart 1—The course of patient "Bar" during amidopyrine, digitan and theocalcin therapy. Mild arthritis is indicated by small blocks on the appropriate line. Intensity of erythema marginatum is indicated by thickness of line marked "Rash."

was sufficient, whereas during the five months before that, 0.9 Gm or more was required. After December 16, a dose of 0.3 Gm kept the patient fever-free, although this small quantity was necessary, as demonstrated after December 31, when it was withdrawn temporarily, and the temperature rose to almost 101 F in two days. The extent to which the activity of the disease has diminished, and consequently the daily dose necessary for effect, can be determined only by such trials.

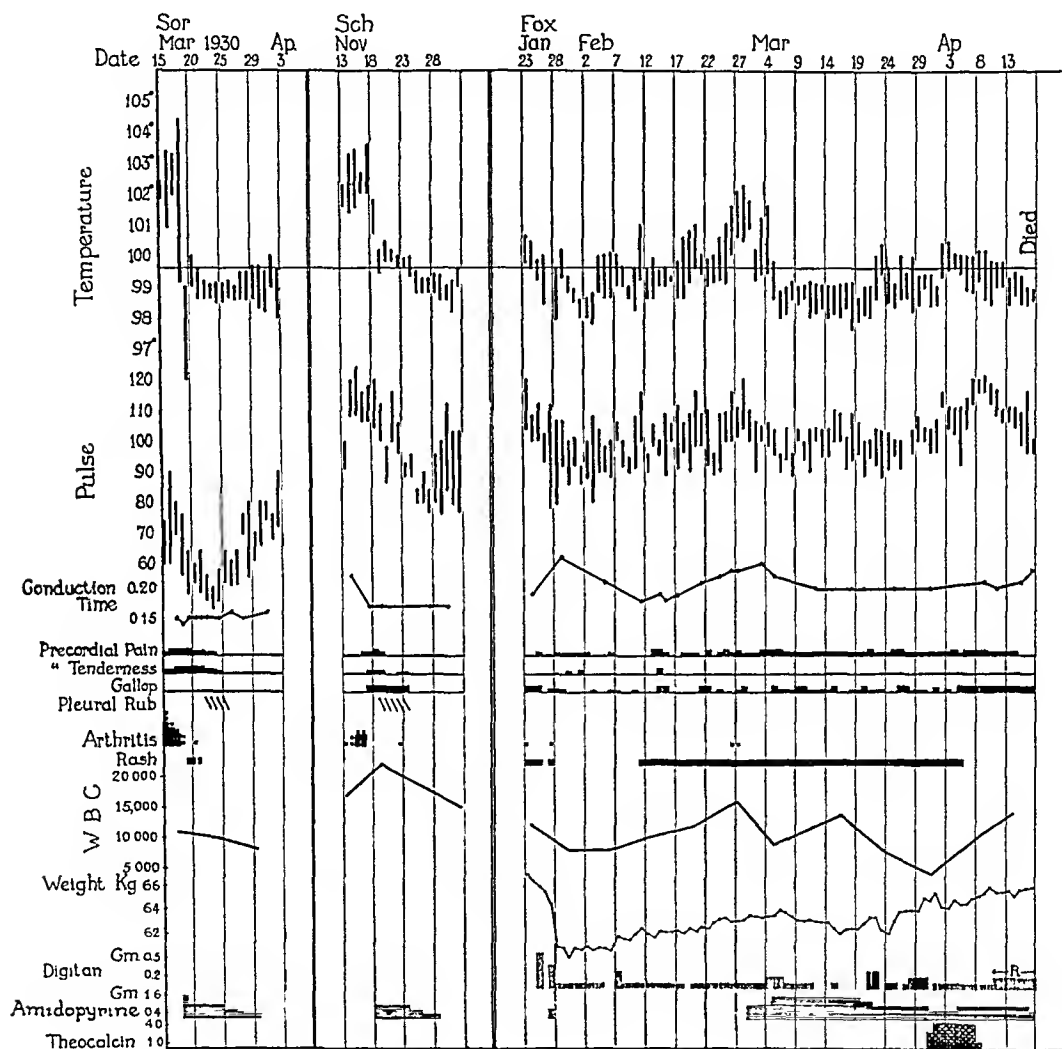


Chart 2—The course of the infection in three patients during amidopyrine medication. Patient "Fox" also received theocalcin and digitan, for the latter drug, "R" indicates rectal administration. Severe arthritis is represented by heavy blocks and mild arthritis by smaller blocks.

During a period of twelve months, amidopyrine was used in this manner in the treatment of thirty-two patients with rheumatic fever. In no instance were the therapeutic results observed to differ from those of other antirheumatic drugs. An analysis of the results yields the following generalizations:

1 Acute attacks of rheumatic fever were relieved by small doses of amidopyrine (from 0.6 to 1.2 Gm daily), which often were reduced or discontinued within a week. Such response in acute involvement was observed in recurrences (four instances) and associated with carditis, pleurisy or pneumonia (seven instances, including the first two cases demonstrated in chart 2, patients "Sol" and "Sch"). Some patients were severely ill, but small doses effectively relieved the symptoms. The tendency to relapse, however, was apparently not modified by this therapy.

TABLE 1—*Effects of Amidopyrine on Two Patients with Rheumatic Fever*

Case	Day of Disease	Daily Dose, Amidopyrine, Gm	Average Temperature Level, F	Arthritic		
				Pain	Tenderness	Swelling
11	37-38	0.00	103.5	+++	++	++
	39	0.90	99.6	++	++	++
	40-41	0.45	100.0	+	++	++
	42-44	0.45	100.0	—	—	++
	45-56	0.45	101.0	—	—	—
	57-59	0.45	100.5	—	—	—
	60	0.45	Normal	—	—	—
	61-73	0.45	100.0	—	—	—
	74-112	0.00	100.0	—	—	—
	210-303	0.00	100.0-101.0	—	—	—
	304-305	0.00	100.0	—	—	—
	306-313	1.50	101.0	—	—	—
	314-350	1.50	100.5	—	—	—
24	6-8	0.00	103.5	+++	++	+++
	9	0.90	101.5	++	++	++
	10-11	0.90	101.0	—	++	++
	12-13	0.90	100.5	—	+	+
	14-15	0.90	101.0	—	++	—
	16-20	1.20	101.6	—	++	—
	21-24	1.80	102.0	+	++	+
	25-27	1.80	100.5	++	+	+
	28-37	1.80	Normal+	++	+	++
	38-43	1.20	100.0	++	+	—
	44-51	1.20	100.0	++	+	—
	52-54	0.90	100.0	++	+	—
	55-65	0.6-0.3	100.0	—	+	—
	66-68	0.00	100.0	—	+	—
	69-72	0.00	100.5	++	+	+
	73-76	0.90	100.0	++	+	++
	77-79	0.9-0.6	Normal	—	++	—
	80-94	0.00	Normal	—	++	—

* ± to ++++ = varying degree of intensity

† — = negative reaction

2 In chronic or subacute phases of the disease, much larger doses (from 0.9 to 2 Gm daily) were usually required over longer periods of time. Case 11, table 1, is an example of this. On admission, the patient, who was severely ill, was relieved and his temperature reduced from 103.5 F to subfebrile levels by doses of 0.45 Gm of amidopyrine daily. Nine months later, when he was perfectly comfortable, although maintaining a fever of 101 F, 1.5 Gm daily did not afford complete antipyresis. Such subacute stages of the disease, relatively refractory to the antipyretic influence of the drug, were more often encountered in recurrences (five cases, including those demonstrated in chart 3, patients

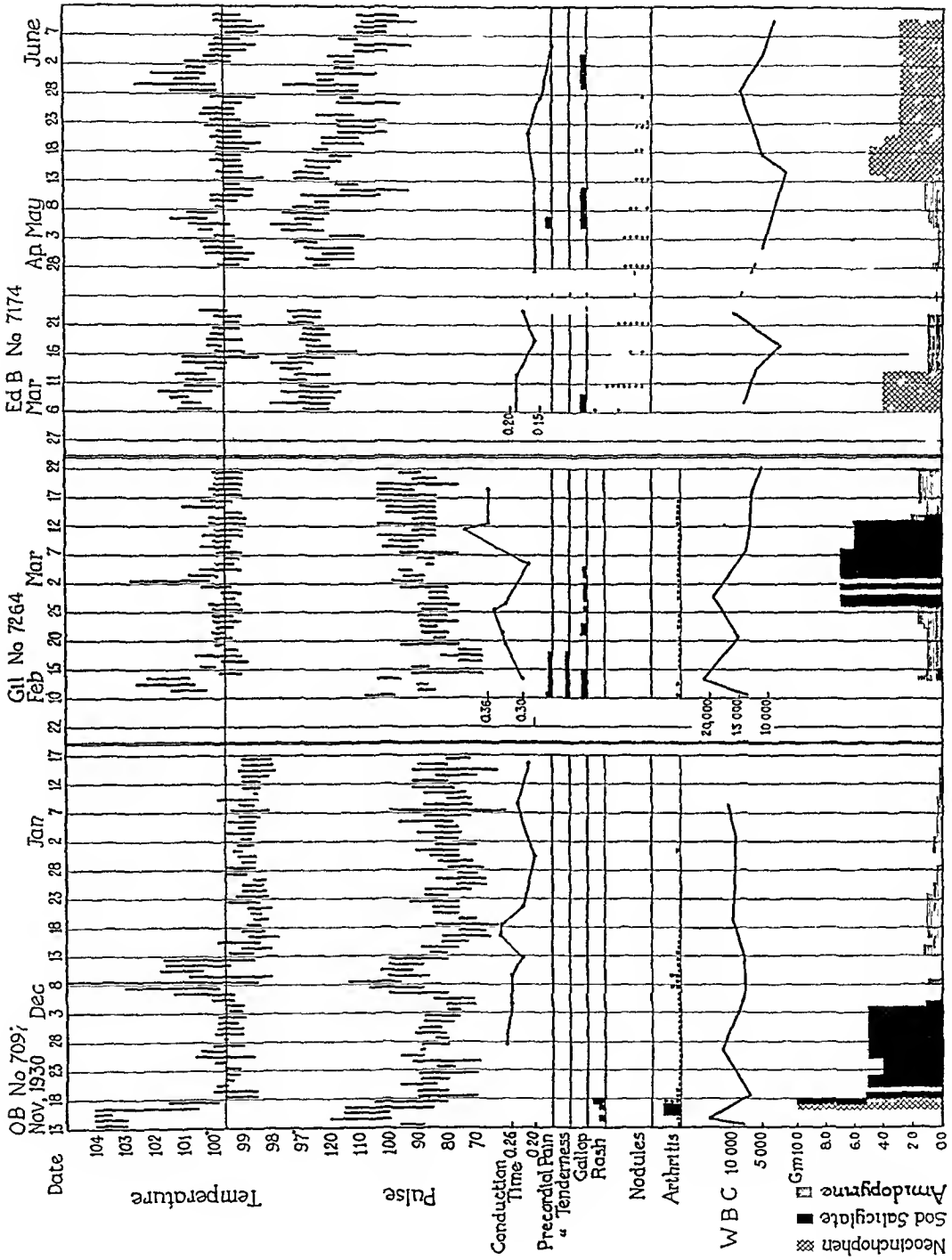


Chart 3—The course of infection in three patients, all of whom during certain intervals received amidopyrine, and during other intervals, sodium salicylate or neocinchophen Arthritis is indicated as in chart 2 In the case of "Ed B" nodules are indicated by solid circles

"Gil" and "Ed B," and in chart 2, patient "Fox") Fundamentally, however, chronicity was the factor that rendered the patient less amenable to the antipyretic effects of the drug

3 Tonsillitis, sinusitis and otitis media were observed in several instances concomitant with active rheumatic fever The temperature elevation due to these infections was less responsive to medication than that exhibited in cycles not so complicated

4 The effects were definitely restricted to antipyresis, analgesia, the lessening of exudation and, possibly, the relief from symptoms of "toxicity" to a degree unaccounted for by antipyresis Thus, fever might be abolished and the pulse slowed when acceleration was not a

TABLE 2—*The Appearance (A), Persistence (P) and Disappearance (D) of Various Evidences of Active Rheumatic Disease While the Patients were Receiving Therapeutic Doses of Amidopyrine*

Case	Rheumatic Erythema Margi- natum	Rheumatic Subacute Nodules	Pleural Rub	Gallop Rhythm	Precordial Pain and Tenderness	Peri- cardial Rub
1				D	D	D
3	P				D	
4		A P			A	A P
7				P	P	A P
8	P				P	
10				P	P	
11				A P D		A D
15	A P	A P				
19					D	
21			D	D	D	A
23				D	D	P
24				A	D	
25	A	D	A D	A P	A	
26			A D	A P D		
Appeared	2	2	2	3	3	4
Persisted	3	2	0	3	3	3
Disappeared	1	0	3	6	7	2

reflection of carditis Joint pain might be relieved, and precordial pain and tenderness, although due to carditis uninfluenced in its course, were often lessened through the analgesic effect (table 2) Occasionally, serous pericarditis and pleurisy were apparently hastened to their resorption through the anti-exudative action of the drug Joint exudates responded in the same way, but this effect was often more slowly manifest than the relief from pain and tenderness

5 The evolution of pathologic changes of a proliferative nature in the course of the disease was apparently uninfluenced by medication The evidence indicated that carditis was not allayed Gallop rhythm, precordial pain and tenderness and pericardial rub frequently appeared and persisted (table 2) Furthermore, changes in the electrocardiogram (e g, prolonged conduction time, inverted T waves), persistently rapid pulse and the development of murmurs indicating progressive valvular

deformity, together with increasing volume of the heart, were all observed during the course of therapy. Other evidences of persisting inflammatory activity of a proliferative character were not abated. Table 2 indicates the appearance and persistence of nodules, rash and fibrinous pleurisy. In addition to these, the presence of leukocytosis and a downward trend of the weight curve, both valuable indexes of persisting infection, were often not modified by medication.

6 Two of the patients observed had chorea in addition to other rheumatic manifestations. No lessening of the choreic movements was observed with full therapeutic doses of the drug.

7 Tonsillectomy and adenoidectomy were performed in ten instances when the patients were in relatively active stages of rheumatic fever. With therapeutic doses for a few days before and after the operation, relapses, which otherwise probably would have been provoked, did not occur.

One case was encountered in which the symptoms were not adequately relieved by amidopyrine (case 24, table 1). The dose was raised to 1.8 Gm daily. This kept the temperature below 102 F, and it fell almost to normal after a week. Meanwhile, moderate inflammation persisted in the joints. Other drugs were not tried, because the patient was severely ill with carditis, and on previous admission it had been found impossible to secure any degree of comfort whatever in this patient with neocinchophen or sodium salicylate, for dosage was restricted by toxic manifestations.

In several instances (chart 3), the action of another drug was compared with that of amidopyrine. The latter, of course, was effective in much smaller doses. A ratio of 1:6 would roughly express the dose of amidopyrine equivalent to that of sodium salicylate or neocinchophen.

The effectiveness of small doses is not so important, however, as the feasibility of giving full, effective, therapeutic doses without limitations imposed by symptoms of toxicity. This is illustrated by case "O'B" represented in chart 3. The vomiting and abdominal pain provoked by neocinchophen in doses of 10 Gm per day, which were given on the first two days of medication, and which, if continued, might have proved effective, forced reduction to 5 Gm of sodium salicylate daily. This dose over a period of two weeks did not completely control fever or arthritis. Of more importance were the severe symptoms of toxicity provoked at the end of that interval. On discontinuing the drug for a few days, the temperature rapidly rose to 105 F, then, 0.9 Gm of amidopyrine in the course of one day reduced it to below 100 F. Following this, daily doses of 1.2 Gm, shortly reduced to 0.9 Gm, afforded complete relief without giving rise to any toxic symptoms.

Of greatest importance in our experience was the complete absence of side actions and the wide margin between effective therapeutic and

the probable toxic dose. These features rendered the drug particularly valuable in the treatment of patients in whom cardiac decompensation had developed during cycles of rheumatic activity. The entire absence of gastric irritation from amidopyrine permits the identification with certainty of the earliest symptoms of cardiac insufficiency arising from visceral congestion, such as epigastric discomfort and tenderness, nausea and loss of appetite. Furthermore, in the course of combined digitalis and amidopyrine therapy, the degree of digitalization may be controlled with increased certainty, because one is confident that the gastric symptoms provoked are due to the former drug.

The usual single dose given was 0.3 Gm. The largest daily dose was 2.4 Gm. In such relatively small amounts, the drug showed all the therapeutic effects to be expected from medication of this type, while no evidence of toxicity was manifest in any patient. One patient received 0.9 Gm. daily for six months, another 1.5 Gm. daily for one month, and another 1.2 Gm. daily for one and a half months. No gastro-intestinal disturbance, such as anorexia, abdominal pain, vomiting, diarrhea or constipation, could be attributed to it. There were no subjective sensations of dizziness, tinnitus or feeling of fullness in the head. No indications of kidney damage or altered renal secretory function were observed on weekly examinations of the urine. With full doses, a slight atypical reduction of Benedict's solution regularly occurred. In only one instance did the urine become pink on standing, presumably due to the formation of rubizonic acid.

SUMMARY AND CONCLUSIONS

Amidopyrine has been used widely as an effective antipyretic and analgesic in a variety of diseases. Excepting the results in typhoid fever, experience indicates that it may be employed in daily doses of at least 3 Gm. without provoking symptoms of toxicity. Instances of idiosyncrasy are less frequent than with many other drugs of this type.

In rheumatic fever, it has been found effective in patients not relieved by other drugs or unable to tolerate them in therapeutic doses, and total daily doses of less than 2 Gm. have been found adequate in this disease. The feasibility of giving effective quantities without provoking untoward side actions, as well as the wide margin between therapeutic and toxic doses, renders this drug particularly valuable in the treatment of patients with rheumatic fever.

PIGMENT METABOLISM AND DESTRUCTION OF BLOOD IN ADDISON'S (PERNICIOUS) ANEMIA *

R F FARQUHARSON, M B

H BORSOOK, M B

AND

A M GOULDING, M D

TORONTO, CANADA

Since the employment of the liver treatment for pernicious anemia,¹ defective formation rather than increased destruction of blood has been emphasized by Minot and Murphy,² Peabody³ and others as the primary factor in causing the anemia. The chief evidence in support of this view is that the ingestion of adequate amounts of liver is followed in a few days by a sharp rise and fall in reticulocytes, and in a few months by a restoration of the blood picture to normal. Relatively little attention has been given, however, to the fact that within the same time all signs of increased blood destruction also disappear.

Although it has long been known that the excretion of urobilinogen in pernicious anemia is high, no quantitative studies have been reported of the change in the amount of urobilinogen in the feces and urine which follows liver therapy. The results of such a study, complemented by corresponding hematologic observations, are described here. The significance of the observations on pigment metabolism in Addison's "pernicious" anemia is discussed.⁴

The most striking changes following treatment were observed in patients with pernicious anemia in a state of relapse. In these patients the excretion of urobilinogen was found to be many times the normal amount. This excessive excretion was nearly always associated with a serum bilirubin value that was higher than normal, and frequently, but not always, with appreciable amounts of urobilin in the urine. During the reticulocyte crisis induced by the ingestion of adequate amounts of

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¹ From the Department of Medicine and the Department of Biochemistry, University of Toronto, and the Medical Service, Toronto General Hospital

1 Minot, G R, and Murphy, W P. Treatment of Pernicious Anemia by a Special Diet, J A M A **87** 470 (Aug 14) 1926

2 Minot, G R, and Murphy, W P. A Diet Rich in Liver in the Treatment of Pernicious Anemia. Study of 105 Cases, J A M A **89** 759 (Sept 3) 1927

3 Peabody, F W. The Pathology of the Bone Marrow in Pernicious Anemia, Am J Path **3** 179, 1927

4 A preliminary report of this work was published in the Proceedings of the American Society for Clinical Investigation, J Clin Investigation **7** 510, 1929

liver, the excretion of urobilinogen fell sharply to within normal limits and remained at a normal level as long as this treatment was continued. At the time of the reticulocyte crisis, also, the serum bilirubin fell to a normal value, and urobilin ceased to be present in the urine in detectable amounts.

In cases of pernicious anemia with little anemia the excretion of urobilinogen was definitely increased, but it was not as high as in severe cases. Usually there was but little increase in serum bilirubin, and urobilin⁵ was not demonstrable in the urine. Liver therapy in such patients evoked a low reticulocyte response with subsequent disappearance of the macrocytosis and a decrease in the excretion of urobilinogen to normal.

These observations support the following interpretation of the excessive pigment metabolism and of the effect of treatment. The abnormal red blood cells, showing great variation in size and shape with marked microcytosis and poikilocytosis as well as macrocytosis, characteristic of pernicious anemia in the state of relapse, are rapidly destroyed. There is, accordingly, an excessive excretion of urobilinogen associated with hyperbilirubinemia and sometimes with urobilin in the urine.⁵ In the cases showing little anemia there is general macrocytosis but less variation in the size and shape of the red cells. These more uniform large cells have a longer life than the irregular forms present in relapse, but a definitely shorter life than that of normal red blood cells. There is, therefore, only a moderate increase in the excretion of urobilinogen with little change in serum bilirubin and usually no urobilinuria.⁵ In both types of cases following liver therapy the bone marrow produces and supplies to the blood stream cells which become progressively more normal and which are less rapidly destroyed. According to this view, the primary factor in the excessive pigment metabolism is an abnormality of the red blood cells, one of the consequences of which is that they are more rapidly destroyed.

METHODS

The urobilinogen was estimated by the method of Terwen,⁶ except in some of the earlier work, in which a band extinction method was employed. The values given in the tables are those for the stools only.

5 Throughout the paper the term "urobilinogen" is used in referring to the pigment in the stools and "urobilin" for the pigment in the urine. The pigment in the stools was measured as urobilinogen and the urine was tested for urobilin, any urobilinogen present being first oxidized to urobilin. The tests used for urobilin are not sufficiently delicate to detect the small amounts present in normal urine. Hence, it is frequently stated that no urobilin was found in the urine.

6 Terwen, A. J. L. New Method for Quantitative Determination of Urobilin in Urine and Faeces. Preparation and Properties of Pure Urobilin, *Arch. f. klin. Med.* **149**:72, 1925.

as the amount excreted in the urine, even in cases with marked urobilinuria, was seldom as great as 5 per cent of that found in the stool. The presence of urobilin in the urine was detected by the copper sulphate chloroform and zinc acetate methods. Serum bilirubin was estimated by the Thannhauser and Anderson modification of van den Bergh's method as described by McNee and Keefer⁷. Results are expressed in van den Bergh units. Hemoglobin was measured in a Sahli hemoglobinometer corrected for the standard of Haden⁸. The percentage of reticulocytes was obtained by counting the number of reticulocytes among 1,000 red blood cells distributed in various parts of a smear that had been vitally stained with brilliant cresyl blue.

Urobilinogen in Feces Zinc Acetate Method (Band Extinction Method) —

The method employed for the determination of urobilinogen in the stools by the band extinction method was essentially that of Elman and McMaster⁹. The specimen of stool was made up to 1,000 cc with water. A 25 cc aliquot was shaken violently in a mechanical shaker for one hour with 75 cc of acid alcohol (1,600 cc of 95 per cent methylated alcohol and 25 cc of concentrated hydrochloric acid made up to 2,500 cc with distilled water). After shaking for one hour, there were added to 25 cc of the mixture 1 Gm of solid zinc acetate and 25 cc of a saturated solution of zinc acetate in 95 per cent methylated alcohol. The mixture was shaken violently for a few moments and filtered. To the clear filtrate a few drops of tincture of iodine were added to convert the remaining urobilinogen to urobilin. It was not found necessary to leave the mixture of stool and acid alcohol standing overnight in order to permit the oxidation of the urobilinogen to urobilin. The same results were obtained whether the determination of the urobilin was carried out immediately after extraction or twenty-four hours later.

The determination of the urobilin content consisted of the dilution of the filtrate containing tincture of iodine and already diluted with an equal volume of a solution of saturated zinc acetate, with a standard diluting solution until the characteristic band of urobilin was no longer visible when the solution contained in a 15 mm test tube was viewed with the slit of the spectroscope so adjusted that the strongest Fraunhofer lines of the solar spectrum were just visible. The standard diluting solution was also that of Elman and McMaster, consisting of 2,000 cc of 60 per cent alcohol, containing 50 Gm of zinc acetate and 2 cc of concentrated hydrochloric acid filtered repeatedly until perfectly clear. The amount of urobilin present in the specimen is expressed by the dilution required for the extinction of the band. It was found that this dilution value, by coincidence, corresponded roughly with the excretion of urobilinogen expressed in milligrams as determined by the method and standard of Terwen. This was true especially for the higher concentrations of urobilinogen in the stool.

7 McNee, J. W., and Keefer, C. S. The Clinical Value of the van den Bergh Reaction for Bilirubin in Blood, *Brit. M. J.* **2**: 52, 1925.

8 Haden, R. L. The Normal Hemoglobin Standard, *J. A. M. A.* **79**: 1496 (Oct. 28) 1922.

9 Elman, R., and McMaster, P. D. Studies on Urobilin Physiology and Pathology. I. The Quantitative Determination of Urobilin, *J. Exper. Med.* **41**: 503, 1925.

*Urobilinogen in Feces Terwen's Method*⁶—Most of the estimations of urobilinogen excreted in the feces were made with the method of Terwen. At first the daily specimens, later the specimens for three days, were thoroughly mixed and a 5 Gm aliquot, or more, depending on the concentration of urobilin in the stool, was weighed out on paraffined filter papers. The stool was scraped off the filter paper, ground up in a mortar with distilled air-free water and made up to 50 cc. Fifty cubic centimeters of a 16 per cent solution of ferrous ammonium sulphate was added and then, with continuous stirring, 50 cc of 12 per cent sodium hydroxide. The mixture was transferred to a flask, stoppered so that all air was excluded, and set away in a dark room overnight at room temperature.

At the end of this period the mixture was filtered through a folded filter paper. Two cubic centimeters of the filtrate was transferred to a small separating funnel, from 0.5 to 1 cc of a 20 per cent solution of tartaric acid (to acidify the solution) and 20 cc of ether (which previously had been washed with 30 per cent sodium hydroxide and four times with air-free distilled water) were added. The mixture was shaken violently, approximately sixty times, in the stoppered separatory funnel. Ten cubic centimeters of the supernatant ethereal solution was measured into a second separatory funnel, and a knife point of Ehrlich's aldehyde and 10 drops of concentrated hydrochloric acid were added. This mixture was shaken for exactly one and a half minutes, a small amount of air-free distilled water was added and finally enough saturated sodium acetate, usually 2 cc, to render the solution no longer acid to congo red. After a short period of further violent shaking, the colored compound of urobilinogen with Ehrlich's aldehyde was dissolved in the lower aqueous solution. This was run off. To the remaining supernatant ethereal solution 5 drops of concentrated hydrochloric acid was added and the solution again shaken for one and a half minutes, 1 cc of a saturated sodium acetate solution was added with a little more water, the mixture was again shaken and the colored aqueous solution again run off. This was repeated until there was no significant amount of color in the aqueous solution.

The different fractions of colored solution were joined and diluted until the intensity of color was approximately equal to that of the standard solution. The standard color solution consisted of 10 cc of a 0.05 per cent solution of phenolphthalein in absolute alcohol and 5 cc of saturated sodium carbonate (at room temperature) diluted to 100 cc. The unknown was compared with the standard in the colorimeter. According to Terwen, the intensity of color in the standard solution is equivalent to that of a solution of 0.4 mg of urobilinogen per hundred cubic centimeters. From this value, the total weight, dilution and colorimetric readings were converted to the number of milligrams excreted.

Urobilin in Urine—In the urine, any urobilinogen present was first oxidized to urobilin and its presence as such determined by either the copper sulphate-chloroform or the zinc acetate method, the former method has been used as a routine test in the Toronto General hospital for a number of years since its introduction by Dr F W Rolph. Ten cubic centimeters of urine is acidified with a few drops of 10 per cent acetic acid, and 1 cc of 20 per cent copper sulphate is added to oxidize any urobilinogen present to urobilin. Two cubic centimeters of chloroform is introduced and the tube is allowed to stand overnight. The urobilin passes into the chloroform layer, coloring it yellowish to pink depending on the acidity. The characteristic band is seen in the spectrum. The zinc acetate method was frequently used in addition. The two tests are about equally sensitive and neither gives a positive reading with normal urine.

METHODS AND TREATMENT USED IN THE WARD

The stools were collected daily and kept in covered cardboard boxes. At first the determinations of urobilinogen were made every day. Later it was found that the value for the mixed stools of three consecutive days was essentially the same as the sum of the three separate determinations. From this time on the stools were mixed in three day periods. In order to secure stools as regularly as possible frequent small doses of cascara were given when necessary. In some cases of combined degeneration of the spinal cord it was especially difficult to obtain daily specimens even with the employment of cathartics. In such circumstances, when there was no stool on a given day, a small saline enema was administered the following morning. In spite of these precautions, there was considerable variation in the weight and urobilin content of the grouped three day stools of these patients.

In nearly all the cases reported here the daily intake of fat, carbohydrate and protein was kept constant throughout the period of observation, and in some cases the same articles of food were given each day. Toward the end of this study when it had become clear that the diet was not an important factor in the excretion of urobilinogen, greater variety was allowed.

After periods of observation of varying length, depending on the patient's condition, some form of liver therapy was administered. One patient received the Eli Lilly extract derived from 300 Gm. of whole liver, some were given cooked whole liver in amounts varying from 100 to 300 Gm. daily, and others were given the juice expressed under pressure from minced whole liver that had been steamed for one-half hour. The latter preparation, which has been in common use in this hospital, is easily taken, and when the juice from 300 to 600 Gm. is given daily, a good reticulocyte response is induced. In two cases, a period in which ineffective extracts were given preceded adequate liver therapy. In most instances dilute hydrochloric acid was not prescribed.

The urobilinogen excretion of a number of normal young physicians and several patients with chronic neurologic disease was also determined. Of the latter group none had any symptoms or signs of disease of the liver or blood-forming organs, and all were in a state of good nutrition and good general health. One of them received a high fat, low carbohydrate diet, another was given in four successive periods, each of from ten to fourteen days' duration, the ordinary ward diet and diets high in carbohydrate, protein and fat, respectively. The results showed clearly that even these radical changes in diet did not alter the amount of urobilinogen excreted.

In order to observe the changes in pigment metabolism in conditions in which increased destruction of blood is known to occur, the excretion of urobilinogen was followed in a case of polycythemia vera treated

vigorously with phenylhydrazine and in a case of dementia paralytica treated with malaria. Concomitant observations of serum bilirubin, red blood cells, white blood cells and hemoglobin were made before, during and after treatment.

REPORT OF CASES

Cases of Pernicious Anemia in Relapse—CASE 1—M G, the patient, aged 59, had a typical case of pernicious anemia and had been ill for four or five years. On admission in his third severe relapse he was weak and

TABLE 1—Results of Liver Therapy in Case 1*

Date	Hemo- globin, per Cent	Red Blood Cells, Millions	Reticu- locytes, per Cent of Red Blood Cells	Serum Bilirubin, van den Bergh Units	Urobi- linogen in Feces, Mg Daily	Urobilin in Urine
June, 1929						
9	24	1.0		2.9		0
17				3.4	340	0
18	23	0.8	1.6		340	0
19					340	0
20				2.2	444	0
21					444	0
22			1.2		444	0
23			1.7		196	0
Liver begun						
24				3.0	196	0
25					196	0
26					423	0
27				2.6	423	0
28					423	0
29			9.2		296	0
30			10.8		296	0
July, 1929						
1	42		10.4		80	0
2	53	2.8	6.2	1.3	80	0
3					80	0
4			3.4	1.0	148	0
5			3.0		148	0
6			2.3		148	0
7	51	2.6	2.1		132	0
8				1.5	132	0
9					132	0
10	50	2.2	1.2		60	0
11	64	2.7			60	0
12					60	0
13					56	0
14					56	0
15	67	2.8	0.5	0.6	56	0

* M G, 67 kg. in weight, with a severe case of pernicious anemia, was treated with 100 Gm of whole liver daily, beginning on June 21, 1929.

pale and had a slight icteric tint. The hemoglobin content was 24 per cent, and the red blood cell count, 1,000,000, the blood smear showed the marked macrocytosis, microcytosis and poikilocytosis characteristic of the state of relapse. He was given daily the rather small dose of 100 Gm of cooked whole liver, which nevertheless induced a definite reticulocyte response. Observations were begun one week before the administration of liver and were carried on during the first three weeks of this treatment. The results are shown in table 1 and chart 1.

The striking feature here, found also in other severe cases of pernicious anemia, is the sharp change in the excretion of urobilinogen. Initially there was a very great output of urobilinogen, which persisted after the beginning of liver therapy until the appearance of the reticulo-

cyte response Beginning at about the peak of this response the excretion of urobilinogen fell sharply to normal within a few days Initially the serum biliubin was also increased and it, too, fell to normal during the reticulocyte crisis It is noteworthy that this excessive excretion of urobilinogen in the stools and the definite increase in serum bilirubin were not accompanied by the excretion of demonstrable amounts of urobilin in the urine

CASE 2—A G, the patient, aged 59, had been treated in the hospital in 1928 during a former severe relapse At that time, although the stools were collected irregularly, there was a tremendous excretion of urobilin associated with a definite increase in serum bilirubin, but demonstrable amounts of urobilin occurred

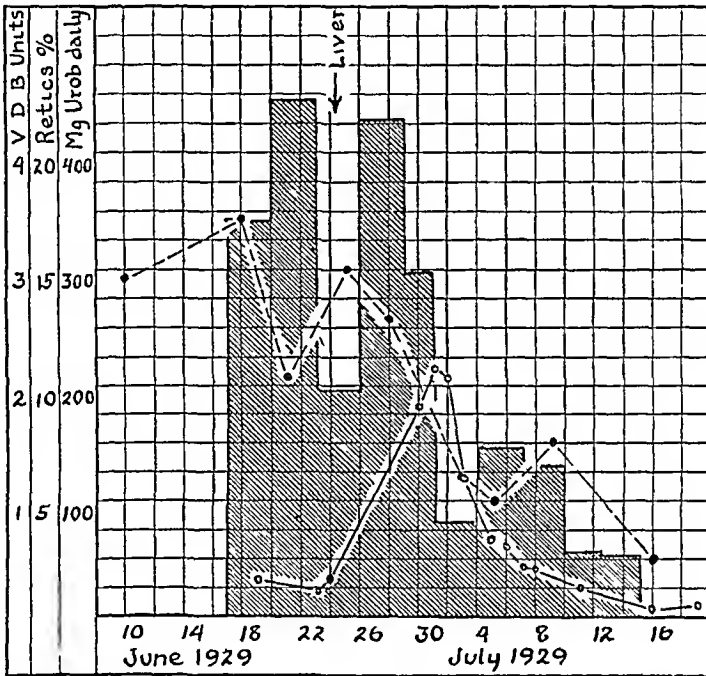


Chart 1—Results in case of pernicious anemia in severe relapse (case 1, M G, showing hemoglobin 24 per cent, red blood cells 1,000,000 and white blood cells 2,000) In this and the following charts, the broken line indicates the serum bilirubin in van den Bergh units, the solid line, percentage of reticulocytes, and the cross-hatched area, milligrams of urobilinogen in the stool daily

in the urine only on rare occasions He responded well to treatment and was discharged in April, 1928, with a hemoglobin content of 75 per cent, red blood cells numbering 3,600,000, a normal excretion of urobilinogen and a normal reaction of the serum to the van den Bergh test He ceased to take liver a few days after his discharge, and he returned to the hospital in a severe relapse on Jan 1, 1929 After a seven day observation period he was given, for fourteen days, a liver extract that proved to be ineffective During this two weeks he became worse, although there was a slight increase in reticulocytes The juice expressed from 800 Gm of liver was then given daily He responded well with a high percentage of reticulocytes and corresponding general improvement The results are shown in table 2 and chart 2

The excretion of urobilinogen and the serum bilirubin values before treatment were highest in this series. Toward the latter part of the reticulocyte response the serum bilirubin fell abruptly. Unfortunately the stools were lost for the few days just at the time that adequate liver

TABLE 2—Results of Liver Therapy in Case 2¹

Date	Hemo- globin, per Cent	Red Blood Cells, Millions	Reticu- loeytes, per Cent of Red Blood Cells	Urobi- linogen in Feces, Mg Daily	Serum Bilirubin, van den Bergh Units	Urobilin in Urine	Non protein Nitro- gen
January 2, 3, 4, 5	32	1.2	0.6	720	3.2	++ trace 0	
6, 7, 8				312	5.6	0	45
9, 10, 11	33 30	1.5 1.2	0.3 0.7	588	3.6	trace	
12, 13, 14, 15	26	1.2	0.2	450	1.0	0 trace	
16, 17			1.1 1.2	Patient incontin- ent, some stools lost	3.8	++	77
18, 19, 20, 21	22		1.8 1.2 1.6		5.2	++ ++	66
22, 23, 24	21		1.1		6.0	+++	65
25, 26, 27	26 29	1.3	2.8 6.0		5.2	+++	40
28, 29, 30	25 10	1.6 2.1	39 40 23	72	1.0 1.8 2.6	++	40
31, February 1, 2	41 30	2.7	1.2 2.4	52	1.1	++ trace 0	
February 3, 4, 5			1.2	248	0.8	0	
6, 7, 8, 9	52	2.5	1.1	52	0.8	0	
10, 11, 12, 13	51	3.9	0.6	32	1.0	0	
Interval, 3 weeks							
March 5, 6, 7	62			21	0.6	0	
8, 9				44		0	
10, 11				36	0.6	0	
12, 13, 14	61	1.3		61		0	
15, 16				68		0	

* A G, 77 Kg in weight, with pernicious anemia, was in severe relapse. From Jan 8 to 21, 1929, he was given an ineffective extract. Beginning on January 22, he received the juice expressed from 800 Gm of liver daily. The results are tabulated in periods, usually of three days each, during which all stools were mixed for urobilin determination. When any of the other values changed materially during a given period the daily values for that period are given in order from above downward in the appropriate column.

therapy was begun. The curves show, however, that the excretion of urobilinogen had decreased before the peak of the reticulocyte crisis. Ten days after the first administration of "liver juice" the urobilinogen excreted was about one-tenth its initial value, and this low level was maintained six weeks after the termination of the reticulocyte response.

In this case there was a striking increase in the amount of urobilin in the urine when the patient became worse during the administration of the ineffective extract. At the same time, the serum bilirubin increased, the blood nonprotein nitrogen rose from 45 to 65 mg per hundred cubic centimeters, the bleeding time was prolonged and purpura appeared, the heart was dilated and the liver enlarged. The patient became extremely ill, stuporous and somewhat incontinent of urine and feces. Although

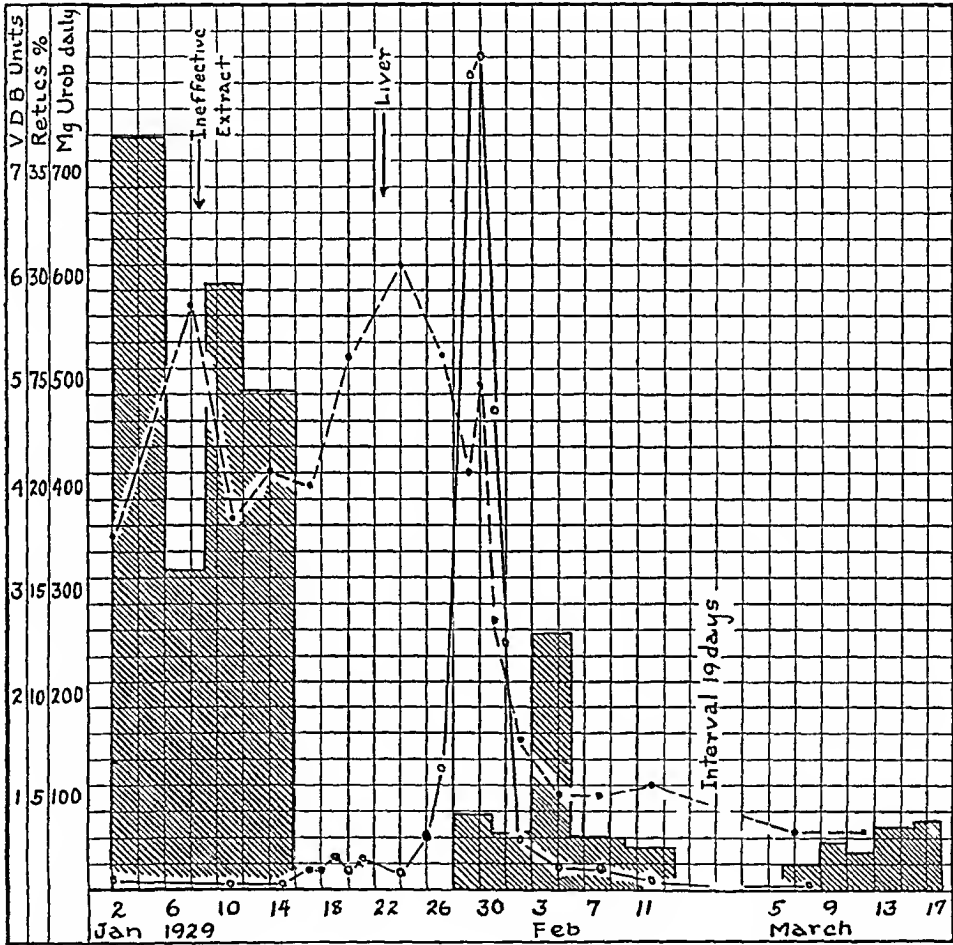


Chart 2—Results in case of pernicious anemia in severe relapse, in which an ineffective extract and then adequate liver therapy were given (case 2, A G, showing hemoglobin 32 per cent, red blood cells 1,200,000 and white blood cells 5,400)

many factors had changed, it is probable that the increased urobilinuria is to be attributed to the damage to the liver that occurred at this time. During the downward curve of the reticulocyte response the urobilinuria ceased and, at the same time, there was general improvement in the condition of the patient: his mental state cleared, he improved quickly in strength and sense of well being, the liver became normal in size, bleeding time decreased and purpura disappeared, the nonprotein nitrogen

and serum bilirubin values fell to normal and henceforth favorable progress continued

CASE 3—A F, the patient, aged 82, had suffered from slowly increasing weakness and lack of energy for two or three years. In the last three months before her admission to the hospital, on Oct 10, 1928, she became much worse. There were marked pallor, great weakness, generalized edema and drowsiness.

CASE 3—Results of Liver Therapy in Case 3*

Date, 1928	Hemo- globin, per Cent	Red Blood Cells, Millions	Reticu- loeytes, per Cent of Red Blood Cells	Urobil- inogen in Tees, Mg Daily	Serum Bilirubin	Urobilin in Urine
October 11	18	0.9				
16	22		3.0			
18, 19, 20	25	1.0		204	2.2	trace
21, 22, 23	28	1.0	1.4	356		0
24, 25, 26	30	1.3	2.8 5.8	320	2.8	+
						0
27, 28, 29	34	1.5	3.8 6.3 9.5	284		0 + ++
30, 31, Nov 1	32 35	1.3	4.5 6.6 1.5	236	3.2	++ ++ ++
November 2, 3, 4	40	1.9	4.4 8.2 15.9	108	0.6	++ + trace
5, 6, 7	40 48	1.6 2.0 2.4	17.0 19.2 9.6	160	0.6	trace 0 0
8, 9, 10	50 54	2.5	6.5 4.0 1.4	80		0
11, 12, 14	51	2.5	1.6 1.4 0.9 0.7	64	0.6	0
Interval, 10 weeks						
1929						
January 25, 26, 27	76	4.6	1.4	112		
28, 29, 30				112		
31, Feb 1, 2, 3	70	4.2	1.2	76		

* A F, aged 82 years, 40 kg in weight, had pernicious anemia. She was improving in a spontaneous remission when an acute otitis media developed, on Oct 28, 1928. Beginning October 29, she was given daily an extract of 300 Gm of liver. The results are tabulated in three day periods. When values changed daily the values for each day of a given period are given in order, from above downward, in the corresponding column, otherwise, just one figure is given for the three day period.

The hemoglobin content was 18 per cent, and the red blood cells numbered 900,000. She improved spontaneously and by the time liver treatment was given, the hemoglobin had risen to 34 per cent and the reticulocytes to 6.3 per cent of the red cells. At this time an acute otitis media developed and her condition became serious. She was given an extract of 300 Gm of liver daily. After a few days there was a further sharp increase in reticulocytes to 19.2 per cent. The otitis media subsided following paracentesis and the patient improved rapidly. The results are summarized in table 3 and chart 3. This patient made an excellent recovery and now after more than one year on liver therapy she continues to feel well.

An interesting feature of this case is that, in spite of a definite spontaneous increase in reticulocytes and an increasing concentration of hemoglobin the excretion of urobilinogen was great and remained so until just before the reticulocytes rose to a much higher level following the administration of liver extract. During this induced reticulocyte crisis, the excretion of urobilinogen fell to normal.

The output of urobilinogen in this instance was, however, less than that in equally severe cases in which there was no spontaneous increase in reticulocytes and in which the hemoglobin was either stationary or falling. In this case, also, the urobilin in the urine definitely increased when the patient became quite ill with otitis media and disappeared at

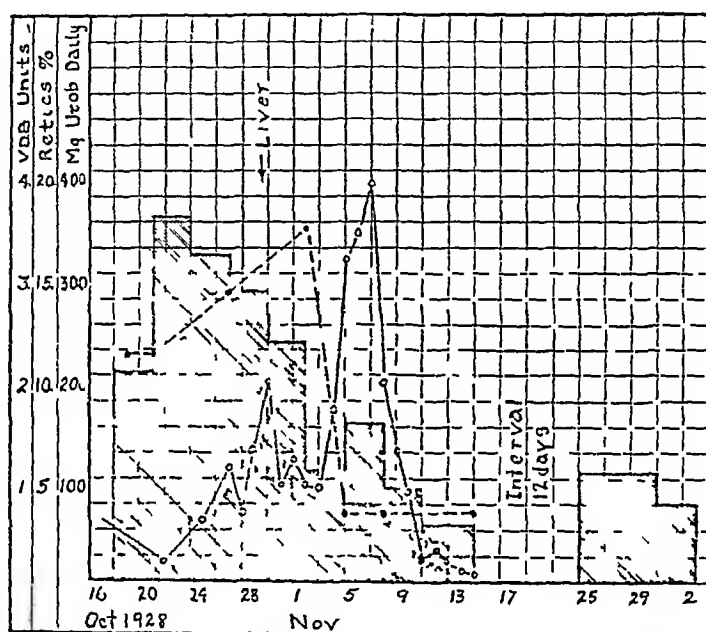


Chart 3—Results in case of pernicious anemia in severe relapse in woman, aged 82, with spontaneous reticulocyte response (case 3, A F, showing initially hemoglobin 18 per cent, red blood cells 900,000 and white blood cells 4,500)

the peak of the reticulocyte response. Three months after the beginning of liver treatment the output of urobilinogen was still within the normal limits.

In table 4 are presented values for the excretion of urobilinogen, van den Bergh test of the serum, reticulocyte percentage and red blood cell count in four other cases (cases 4, 5, 6 and 7) of severe pernicious anemia before and during the first few weeks of liver treatment. In all four cases there was an initial very great output of urobilinogen, which fell off sharply during the reticulocyte response. The serum bilirubin also reached normal levels during this period, and urobilinuria when present, disappeared before the end of the crisis.

It is interesting to note the absence of parallelism between the values for fecal urobilinogen and serum bilirubin and the presence of urobilin in the urine. With a fecal urobilinogen output of 493 mg daily, case 4 showed a slight increase in serum bilirubin, and a trace of urobilin in the urine on one occasion only. The initial serum bilirubin in G M (case 6),

TABLE 4—Summary of Results in Four Cases of Pernicious Anemia in Relapse*

Day	Case 4 (C. J., Aged 62, Weight, 53 kg)†					Case 5 (W. C., Aged 16, Weight, 61 kg)‡					Case 6 (G. M., Aged 46, Weight, 60 kg)§					Case 7 (G. D., Aged 53, Weight, 57 kg)¶				
	Urobilinogen in Feces, Mg Daily	Urine Urobilin	Serum Bilirubin	Red Blood Cells, Millions	Reticulocytes, per Cent	Urobilinogen in Feces, Mg Daily	Urine Urobilin	Serum Bilirubin	Red Blood Cells, Millions	Reticulocytes, per Cent	Urobilinogen in Feces, Mg Daily	Urine Urobilin	Serum Bilirubin	Red Blood Cells, Millions	Reticulocytes, per Cent	Urobilinogen in Feces, Mg Daily	Urine Urobilin	Serum Bilirubin	Red Blood Cells, Millions	Reticulocytes, per Cent
Av §			17	19	<0.3	376	to 0	17	12	<0.3	39	+	22	0.75	0.3	469	+	15	11	<0.2
1						140	0				46	+		0.6	0.3	416	+			
2						110	trace		17	0.15	39	+				636	+		11	<0.3
3	493	0			0.4	440	trace				46	+				636	+			
4	493	0	12	16	0.2	264		20			26	+		0.6	0.4	636	++			0.9
5	493	0		12	0.2	264	0				180	+	10		0.2	636	trace			0.3
6	341	0		10	0	264	0		17	0.5	180	+		10	0.5	360	+		10	0.3
7	341	0		13	0	132	0				160	+		12	0.3	360	++	16		0.3
8	341	trace	07	12	11.6	132	0			5.0	176	+++			0.2	360	++			1.0
9	155	0		16		152	0				176	+	18	16	0.2	192	++			0.8
10	155	0		24		132	0		23	12	268	+			0.15	192	+		10	1.2
11	91	0		24	2.0	132	0	16			268	+				192	trace	11		0.9
12	91	0		26	2.2	132	0				4	+	12		0.2	176	+++			0.8
13	91	0		28	2.0	80	0				56	+		18	0.5	176	+++		10	1.8
14	91	0				80	0	0.6	25	10	56	+				176	++			2.8
15	112	0		29	0.8	68	0				56	+		21		232	+++			2.8
16	112	0		14		68	0				168	+	0.5			232	++			1.6
17	112	0				68	0			2.5	168	trace			1.3	232			12	2.3
18	85	0		0.2		68	0	0.6			168	0	0.6			212	0	10	15	3.3
19	85	0		0.2		128	0		12		11	0				212	0			2.0
20	85	0				128	0				41	0				61	0			
21	125	0				128	0				41	0				61	0		22	5
22	125	0				72	0		15	0.2	68	0				61	0	0.6		
23	125	0				72	0				68	0				61	0		25	5.5
24	91	0				72	0				68	0	0.6		0.2	48	0			3.2
25	91	0		0.2		72	0	0.6			30	0				48	0	10	25	2.8
26	91	0				72	0				30	0				48	0			<1
27	78	0					0				40	0		3.6	0.1	52	0			
28	78	0					0				81	0				52	0			
29	78	0					0				81	0				52	0			
30	42	0					0				81	0	0.6			72	0			1.0
31	42	0					0				2	0								
32	38	0		4.5	<0.2						32	0					0	0.6	3.5	0.6

§ Average value in control period

* The first line of figures gives the average value obtained before the beginning of liver therapy. In the second line are the values obtained for the first day on which liver was given, and succeeding lines in order are for succeeding days.

† This patient, a moderately severe case of pernicious anemia, was treated daily with 111 Lilly liver extract made from 300 Gm of liver in June and July, 1927. In this case estimations of urobilin were made by the band method. All the others in this table were made by the Terwen method.

‡ This patient, in fairly severe relapse, was treated with the juice from 1,000 Gm of liver daily in May, 1929, until the twelfth day, from then on he was given the juice of 600 Gm of liver daily.

§ This patient was in his second severe relapse, and was very ill. He was treated with juice from 1,500 Gm of liver daily for the first eleven days, then juice from 1,000 Gm daily.

¶ This patient had a typical severe relapse. He was given first an inadequate extract for eleven days, then, from the twelfth day on, 300 Gm of whole liver plus juice from 600 Gm of liver daily. Showed rapid improvement.

who was seriously ill on admission and became much worse in the next few days, was 22 units. It rose to 40 units. His urine gave strong tests for urobilin. G D (case 7) with a very great fecal urobilinogen excretion also showed considerable amounts of urobilin in the urine, but his serum bilirubin did not rise at any time above 2 units. Like G M, he was also seriously ill.

In a much larger series of cases than are reported here it has been common to find serum bilirubin values ranging from 2 to 4 units in patients with pernicious anemia in relapse. Large amounts of urobilin in the urine have been found only in those patients who were exceptionally ill, as in cases 2, 3, 6 and 7 of this series.

These cases of pernicious anemia in relapse show with striking regularity the rapid decrease in a high excretion of urobilinogen coincident with the latter part of the reticulocyte response. Beginning at about this time also the proportion of reticulated cells of normal size increases rapidly and the extremely large, as well as the very small and deformed cells in the smear become progressively fewer, so that by the time the reticulocytes have fallen to less than 2 per cent of the red blood cells the smear presents a much more normal appearance. In many instances also the color index at this stage has fallen to less than 1.

So rapid a disappearance of the grossly abnormal cells must, it seems, be due to actual destruction. There are no reasons for believing that they could be transformed so quickly into cells of nearly normal size and shape. On the other hand, the view that they have been destroyed is supported by the constant association of a high urobilinogen excretion with the presence of marked variation in the size and shape of the majority of the red blood cells, by the sharp drop in excretion of urobilinogen as the red blood cells rapidly become more normal in appearance, and by the persistence of a normal output while the hemoglobin and red blood cells increase and so long as normal values are maintained.

Cases of Pernicious Anemia with Little Anemia Frequently Presenting Symptoms and Signs of Subacute Combined Degeneration of the Spinal Cord—A number of cases of pernicious anemia were observed at periods of the disease when the hemoglobin and red blood cells had not fallen to very low levels. Such patients frequently complained of symptoms of subacute combined degeneration of the cord, although a few suffered chiefly from increasing weakness before there was any well marked degree of anemia. The blood smear usually showed a general macrocytosis with few microcytes or poikilocytes. The blood picture, however, varied in degree from a condition of mild anemia and general fairly uniform macrocytosis to a state of moderate anemia with increasing microcytosis and poikilocytosis. The excretion of urobilinogen and, to some extent, the serum bilirubin also varied correspondingly. In none of this group was there any appreciable amount of urobilin in the urine.

CASE 8—H. S., the patient, aged 67, had been treated in the hospital in 1926 for pernicious anemia in severe relapse. Since discharge he had taken liver irregularly, never in adequate amounts. For some months before readmission on Oct. 26, 1928, he had suffered from weakness, lack of energy, and numbness and tingling of the hands and feet. His condition was relatively stationary during a

preliminary period of three weeks, his hemoglobin averaging 63 per cent. He was then given daily the juice expressed from 600 Gm of liver. There followed a low reticulocyte response with definite clinical improvement and a gradual rise of the hemoglobin and red blood cells to normal. The results are presented in table 5 and chart 4.

The initial excretion of urobilinogen was definitely above the upper limit of normal, the serum bilirubin was normal, and there was no urobilin in the urine. During the reticulocyte response the urobilinogen output decreased somewhat, but after more than a month of liver therapy

TABLE 5—Results of Liver Therapy in Case 8*

Date	Hemo- globin, per Cent	Red Blood Cells, Millions	Reticu- locytes, per Cent of Red Blood Cells	Urobi- linogen in Urine, Mg Daily	Serum Bilirubin, van den Bergh Units	Urobilin in Urine
October 27	65	2.5	Rare		0.8	
30, 31, Nov 1				112		0
November 2, 3, 4	71	3.0	0.1	212		0
5, 6, 7	63	2.6	0.2	228		0
8, 9, 10	60	2.3	0.2	284	0.6	0
11, 12, 13	58	2.3	0.3	196		0
14, 15, 16	64		0.2	240		0
17, 18, 19	60		0.4	204		
20, 21, 22				232		
23, 24, 25	58	2.4		120		0
26, 27, 28			0.4	236		0
29, 30, Dec 1	68	2.1	4.0	160		
December 2, 3, 4	61	2.5	7.0	80		
5, 6, 7	62	3.1	2.8	100		
8, 9, 10	71	3.3	2.2			
Interval, 7 days						
December 18, 19, 20				162		0
24, 25, 26	84	4.7	0.1	140		0
27, 28, 29				48		0
30, 31, Jan 1, 2				144		0
Interval, 4½ months						
1929						
May 17, 18, 19	80	5.1	Rare	132	0.6	0
20, 21, 22				36		
24, 25, 26				68		
27, 28				80	0.5	0

* H. S., 54 Kg. in weight, had pernicious anemia with slight anemia, he was treated with the juice expressed from 600 Gm of liver daily, beginning on Nov. 26, 1928.

it was still at a rather high level. A slight but definite macrocytosis persisted. Five months later, when the blood smear was normal, the excretion of urobilinogen had fallen to an average normal level.

In table 6 are presented data obtained from the three following cases of pernicious anemia with subacute combined degeneration of the spinal cord.

CASE 9—H. D. had become unable to walk before the development of the anemia. On admission to the hospital his hemoglobin was 78 per cent, the red blood cells numbered 3,300,000 and the smear showed a well marked macrocytosis. He was obstinately constipated and the stools obtained with purgatives and enemas varied greatly in size. Before liver therapy the average daily output of urobilinogen in a twelve day control period was 195 mg. After a low reticulocyte

response the average for fifteen days was 114 mg. At the end of this time a slight anisocytosis persisted although the majority of the cells were normal in size. Later, when the blood smear was normal there was no opportunity to measure the excretion of urobilinogen.

CASE 10—J W was admitted with a complaint of difficulty in walking. He had been under liver therapy for over two years, during most of which time he was well. For many months, however, to save expense he had taken the extract of only one-third pound (151 Gm) of liver daily. Even on this small dose he felt well until two months before admission, when stiffness and unsteadiness in walking began. His gait became progressively worse and he also suffered from some general weakness and lack of energy. On admission to the hospital his hemoglobin was 70 per cent and the red blood cell count, 2,700,000. The smear showed a definite anisocytosis with frequent large polychromatic cells, many normal-sized cells and some microcytes. Following the daily administration of

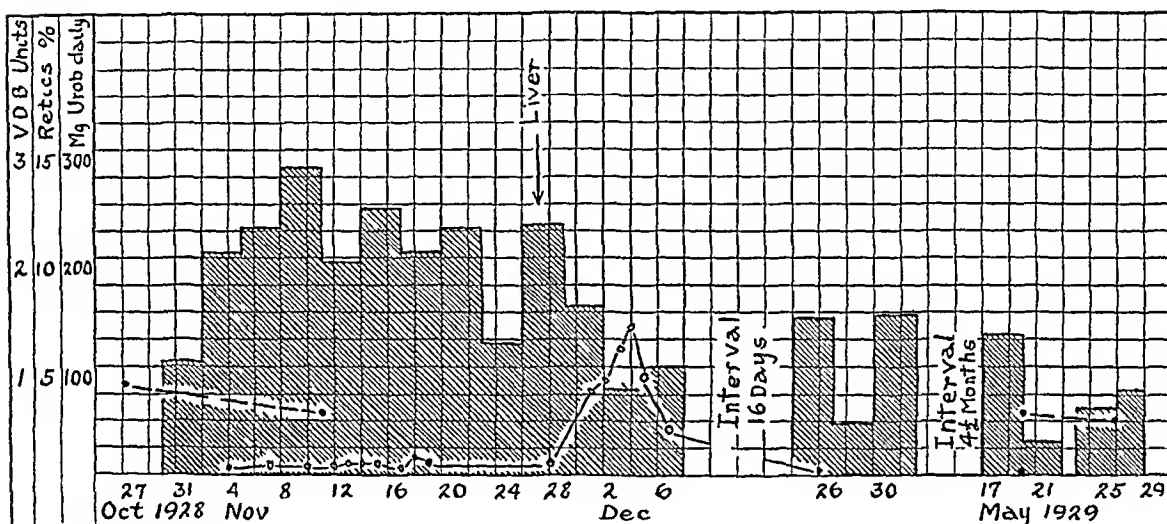


Chart 4—Results in case of pernicious anemia (case 8, H S, showing hemoglobin 65 per cent, red blood cells 2,500,000 and white blood cells 5,200)

the juice from 800 Gm of liver, he improved greatly in general strength and sense of well-being, the reticulocytes fell to less than 0.5 per cent and the hemoglobin and red blood cells rose to normal. The excretion of urobilinogen could not be measured for more than two days before liver was given. An estimate of the quantity of urobilinogen excreted before treatment was obtained by averaging the output for these two days with that of the next four days, which gave the value of 244 mg per day. Then followed a rapid decline to less than 100 mg per day, at the same time the abnormal conformation of the red blood cells became much less marked.

CASE 11—On admission to the hospital, W O presented a typical picture of severe combined degeneration of the spinal cord with general weakness and lack of energy and a moderate degree of anemia. His hemoglobin was 59 per cent, the red blood cell count, 2,800,000. There was marked variation in the size and shape of the red cells with well marked macrocytosis and definite microcytosis, the blood picture of pernicious anemia in relapse. Following the daily ingestion

of the juice expressed from 600 Gm of whole liver, the reticulocytes rose to a peak of 20 per cent on the eighth day, by which time most of the reticulocytes were of normal size. The urobilinogen of the feces, measured by the band method, fell from an initial level of almost 300 mg daily to less than 75 mg daily after

TABLE 6—Summary of Results in Three Cases of Pernicious Anemia with Subacute Combined Degeneration of the Cord and Mild or Moderate Anemia¹

Day	Case 9 (H. D., Aged 45, Weight, 59 Kg)† Jan 15 to Feb 22, 1929					Case 10 (T. J. W., Aged 39, Weight, 76 Kg)‡ March 13 to April 16, 1929					Case 11 (W. O., Aged 46, Weight, 52 Kg)§ Sept 19 to Oct 22, 1928				
	Urobilinogen in Feces, Mg Daily	Urobilin in Urine	Serum Bilirubin	Red Blood Cells, Millions	Reticulocytes, per Cent	Urobilinogen in Feces, Mg Daily	Urobilin in Urine	Serum Bilirubin	Red Blood Cells, Millions	Reticulocytes, per Cent	Urobilinogen in Feces, Mg Daily	Urobilin in Urine	Serum Bilirubin	Red Blood Cells, Millions	Reticulocytes, per Cent
Avg	195	0	0.6	3.3		0	0	1.8	3.2	1.9	278	trace	2.3	3.0	1.0
1	108	0				168	0	1.8			270		1.6		
2	108		0.6	3.6	0.7	320	0		2.9	1.4	270				<1
3	108				0.3	320	0								
4	216				0.5	320	0	1.6	3.3	1.5	240		1.2		<1
5	216					88	0			1.7	320				2.5
6	216				0.7	88	0			1.4	70				7.0
7	112			1.2	3.6	88	0				110				1.4
8	112				1.6	104	0	0.8		2.0	75		1.2	3.3	2.0
9	112				4.1	104	0				60				2.0
10	44	0			3.3	104	0			1.6	60				1.6
11	44				1.8	88	0	0.8			20		0.8	3.6	1.0
12	44				0.9	88	0		4.1	1.7	30				7.9
13	100					88	0				60				4.0
14	100					44	0				40				<1
15	100			3.8		44	0	1.0			30		0.6		<1
16	72					41	0				30				
17	72					84	0				70				
18	72			3.6	0.4	84	0				100		0.6		
19	228		0.6			84	0				50			4.0	
20	228										90				
21	228										70				
22	76										50				
23	76														
24	76	0						0.6							
25	96														
26	96			3.8					4.6	0.1				4.9	
27	96														
28															
29													0.6		
30								0.8							
31															
32			0.6		0.4										

§ Average value in control period

* As in table 4 the first line of figures gives the average value obtained before the beginning of liver therapy, in the second line are the values for the day on which liver was first given, and in subsequent lines, in order, the values for succeeding days

† This patient had severe disease of the spinal cord and a little anemia. He was treated with 200 Gm of whole liver daily. The red blood cell count rose somewhat slowly to 5,100,000 in two months.

‡ This patient had moderately severe disease of the spinal cord. Beginning March 18, 1929, he was given juice expressed from 800 Gm of liver daily.

§ This case showed severe combined degeneration of the spinal cord, the symptoms and blood picture were those of early relapse. Beginning Sept 24, 1928, the patient received the juice expressed from 600 Gm of liver daily. The urobilinogen determinations in this case were made by the band method, and the figures therefore represent only approximate values.

the reticulocyte response. Although the anemia in this case was not severe, the symptoms and blood picture were those of pernicious anemia in mild relapse. Associated with the greater abnormality in the appearance of the red blood cells, the excretion of urobilinogen was higher than in the two preceding cases. With

a good reticulocyte response the output of urobilinogen fell sharply to normal and, at the same time, the extreme macrocytosis and microcytosis disappeared

A Case of Pernicious Anemia with Severe Anemia and Combined Degeneration of the Cord in Which the Response to Liver Therapy Was Unusually Slow—

CASE 12—J R, the patient, admitted to the hospital on April 13, 1929, had been treated in the hospital on previous occasions for pernicious anemia and chronic bronchitis with pulmonary emphysema. On his discharge in July, 1928, his hemoglobin was 91 per cent, he felt fairly well and was able to work. Since that time he had taken very little liver and after a few months he began to fail gradually in strength, weight, color and sense of well-being. He also suffered from unsteadiness and weakness, which grew worse until he became unable to

TABLE 7—Results of Liver Therapy in Case 12*

Date, 1929	Hemo- globin, per Cent	Red Blood Cells, Millions	Reticu- loeytes, per Cent of Red Blood Cells	Serum Bilirubin, van den Bergh Units	Urobilinogen in Feces, Mg Daily	Urobilin in Urine
April 13, 14	35	1.6	0.1		272	++
15, 16	40	1.4		1.6	292	++
17, 18, 19	30	1.0		1.2	{ 5 days }	++
20, 21	42	1.4	0.1		160	+
22, 23, 24	41	1.7	1.5	1.0	248	++
25, 26, 27, 28	39	1.6	2.0	1.4	64	+
29, 30, May 1, 2	38	1.3	3.2	1.0	88	++
May 3, 4, 5			May 5 5.0		152	+
6, 7, 8, 9	41	1.8	2.0	0.8	236	+
10, 11			0.8		104	trace
12, 13, 14					182	trace
15, 16, 17, 18				0.6	124	0
19, 20				0.6	28	0
21, 22, 23	57	2.7	Rare		{ 5 days }	0
24, 25					100	0
26, 27, 28	64	3.0	0.5	0.6	72	0
Interval, 3 months						
September 9, 10	90	4.9	†		56	0
11, 12					45	0
13, 14, 15					60	0
16, 17, 18					76	0
19, 20, 21, 22, 23					36	0

* J R, weighing 61 kg, had severe pernicious anemia with subacute combined degeneration of the cord. He received the juice from 800 Gm of liver daily, beginning on April 20, 1929. The results are tabulated in periods during which stools were mixed for urobilinogen determinations. Representative values of other factors for each period are given.

† Occasional

walk. He was admitted in a weak condition, presenting signs of advanced subacute combined degeneration of the cord. A summary of important laboratory observations is given in table 7 and chart 5.

His hemoglobin was 35 per cent, the red blood cells numbered 1,560,000, and the smear showed definite but not extreme macrocytosis, microcytosis and poikilocytosis. He was given daily the juice expressed from 800 Gm of whole liver, but the response to such a large dose was small at first and very slow. The reticulocytes reached a peak of only 5 per cent on the fifteenth day and then gradually fell off. After eighteen days of treatment with liver there was still marked macrocytosis and microcytosis and as yet no appreciable increase in the hemoglobin percentage or red blood cell count. In the next few weeks, however, the anisocytosis became much less marked and the hemoglobin and red blood cells began to increase and from this time on the patient improved rapidly.

The response in this instance was similar to that in a case described by Minot, Murphy and Stetson¹⁰ Their patient showed no distinct reticulocyte response and little increase in the red blood cell count in the first six weeks of treatment, but after this period the red blood count rose rapidly to normal

The initial urobilinogen output averaged 229 mg daily, definitely a lower value than is usually found with such a degree of anemia in pernicious anemia. The patient was obstinately constipated, however, and the stools accordingly irregular in size. In spite of this irregularity it is clear that a high urobilinogen output persisted for over three weeks after the institution of liver treatment. As the character of the smear began to change and the hemoglobin and red blood count began to rise,

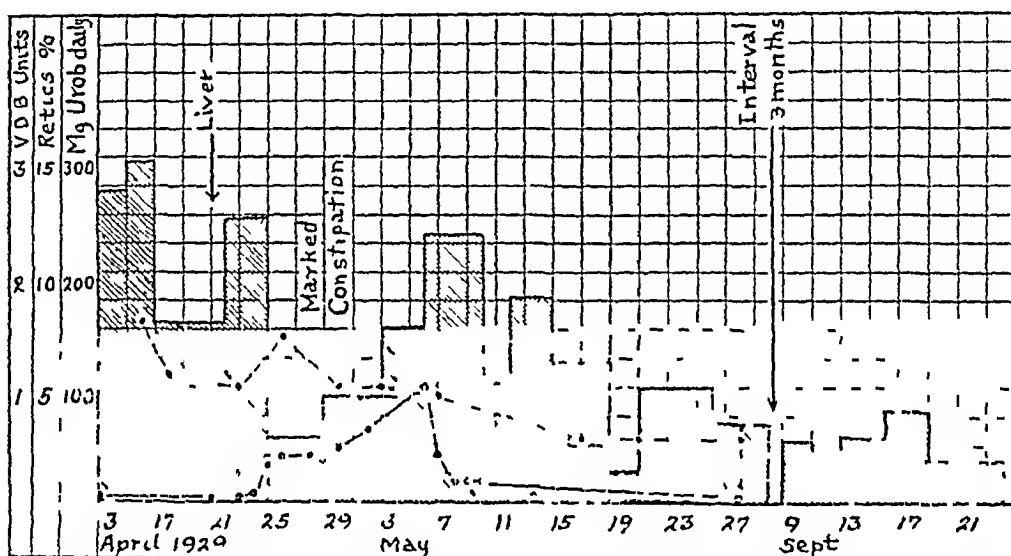


Chart 5—Results in case of pernicious anemia in relapse, with extensive sub-acute combined degeneration of the cord (case 12, J. R., showing initially hemoglobin 35 per cent, red blood cells 1,600,000 and white blood cells 2,100). The hematologic response to liver therapy was slow and the excretion of urobilinogen remained at a high level for a corresponding period.

the excretion of urobilinogen fell to a definitely lower level. Three and one-half months later, when the smear was normal, the hemoglobin 90 per cent and the red blood cell count 4,900,000, the excretion of urobilinogen was well within normal limits.

This case clearly illustrates the relation of the high output of urobilinogen to the grossly abnormal red blood cells. In spite of the ingestion of large amounts of liver the response of the bone marrow was very slow and the smear retained the characteristics of pernicious

10 Minot, G. R., Murphy, W. P., and Stetson, R. P. The Response of the Reticulocytes to Liver Therapy, Particularly in Pernicious Anemia, *Am J M Sc* 175: 581, 1928.

anemia As long as the marked anisocytosis persisted, the excretion of large amounts of urobilinogen continued When the red blood cells became more normal in appearance in the third and fourth weeks, the output of urobilinogen fell off and the hemoglobin and red blood cell count rose Later, when the red blood cells appeared normal, the excretion of urobilinogen was also normal It may be noted that in this case

TABLE 8—*Urobilinogen Content of the Stool in Five Physicians and Five Neurologic Patients on Various Diets**

Subject	Age	Weight, Kg	Diet	Average per Day, Mg	Urobilinogen in Feces												
					Day												
					1	2	3	4	5	6	7	8	9	10	11	12	13
N M W (normal)	28	65	House physician's†	34	28	28	28	16	16	52	52	52					
E J M (normal)	30	77	House physician's	50	60	60	64	64	8	8	68	68					
R F F (normal)	31	79	House physician's	24	32	32	24	24	16	16	16						
K E F (normal)	29	64	House physician's	52	12	12	12	108	108	56	56	56	56				
T A C (normal)	29	70	House physician's	129	68	68	68	180	180	156	156	156					
J W (tabes dorsalis)	40	55	Ward diet	24	16	16	16	16	16	16	48	48					
H G (muscular dystrophy)	19	60	Ward diet	24	24	24	24	20	20	20	28	28	28				
H O (hemi paresis)	50	55	Ward diet	38	48	48	48	28	28	28							
B L (epilepsy)	26	55	P 40, F 180, C 40 P 40, F 180, C 20	48 64	60 24	60 24	60 76	36 76	36 76	36 80	48 80	48 80	48				
L B (Fried reich's ataxia)	28	16	Ward diet P 40, F 50, C 400 P 140, F 160, C 75 200 Gm of liver, high fat diet P 40 F 200, C 80	55 56 56 56	56 48 72 80	56 48 84 80	40 48 84 48	40 56 84 48	40 56 36 48	72 56 36 48	72 52 48 48	72 52 48 48	52 52 48 48	52 72 36 36	52 72 36 36	80	

* The days are numbered consecutively from the first day on which urobilinogen determinations were made The stools were mixed usually in three day periods, occasionally in two or four day periods

† Ordinary mixed diet

urobilinuria persisted as long as the high excretion of urobilinogen in the feces continued

EXCRETION OF UROBILINOGEN IN OTHER CONDITIONS

In order to appreciate the significance of the excretion of urobilinogen in cases of pernicious anemia, the urobilinogen of the stool was measured in a number of normal persons, in several patients with chronic neurologic diseases but good general health, in one case of polycythemia and in two patients with dementia paralytica in whom malaria was produced for therapeutic purposes

Normal Excretion of Urobilinogen—The values for excretion of urobilinogen of five healthy physicians and five neurologic patients are given in table 8. All ten persons had a normal red blood cell count, a normal percentage of hemoglobin, and normal serum bilirubin (less than 1 unit). None presented symptoms or signs of disease of the liver. None had urobilinuria.

The five physicians took the same ordinary mixed diet. One of them (T. A. C.) had an unusually large excretion of urobilinogen, averaging 128 mg per day and amounting to more than twice that of any of the other controls. No reason for this variation was found. This value, however, lies within the normal range as described by Lichtenstein and Terwen.¹¹

Of the neurologic patients, three were on ordinary ward diet. One was given a diet with a high fat and low carbohydrate content in treatment for epilepsy. The average daily output of urobilinogen in a seventeen day period was 56 mg, a figure well within the normal limit. The other, afflicted with Friedreich's ataxia and lying in bed all the time, was given in succession the ordinary ward diet for eleven days, a diet with a high carbohydrate content for eleven days, a diet with a high protein content, including 200 Gm of whole liver, for thirteen days and a diet with a high fat content for eight days. The average daily excretion for these different periods varied only from 55 to 56 mg, thus showing that radical changes in diet did not affect the output of urobilinogen. It is of especial interest that the ingestion of 200 Gm of whole liver daily by this patient failed to alter the excretion of urobilinogen.

The average daily output of urobilinogen of the ten subjects varied from 24 to 128 mg. In patients with pernicious anemia such values were obtained at or soon after the termination of the reticulocyte response. In the cases studied, the average daily excretion for the last six days of observation was between 50 and 90 mg, and one patient who had been under treatment for two years excreted 36 mg per day in a nine day period.

The variation in the excretion of urobilinogen from period to period in a given person was largely dependent on the size of the stool, but in different persons there was considerable variation in the ratio

$$\frac{\text{Weight of stool, Gm}}{\text{Urobilinogen content, mg}}$$

Induced Destruction of Blood and Excretion of Urobilinogen—It was important to ascertain the effect of induced destruction of blood on the excretion of urobilinogen. An excellent opportunity was pro-

11 Lichtenstein, A., and Terwen, A. J. L. Blood Molting and Excretion of Urobilin, Arch f klin Med 149 102, 1925

vided by a case of polycythemia vera observed before and during treatment with phenylhydrazine

CASE 13—S H, aged 55, presented a typical picture of this condition. On his admission to the hospital, in June, 1927, the red blood cell count was 10,600,000 and the hemoglobin 126 per cent. After observation for one week he was given 0.2 Gm of phenylhydrazine hydrochloride daily for fourteen days. During this time the urobilin content of the stools and urine, the serum bilirubin, the hemo-

TABLE 9—*Observations in a Case of Polycythemia Vera During Treatment with Phenylhydrazine Hydrochloride*

Date 1927	Red Blood Cells, Millions	Hemoglobin, per Cent	White Blood Cells, Thousands	Serum Bilirubin, van den Bergh Units	Urobilin in Stools§	Urobilin in Urine	Corpuscle Volume	Phenylhydrazine, Gm
June 2 ^o					106	0		
24					106	0		
25					106	0		
26	10.6	126			106	0	73	
29	11.1	130			75	0	72	
30	13	125	14.8		75	0		0.2
July 1					75	0		0.2
2	11.9		27		304	0		0.2
3					304	0		0.2
4	9.5	115	13.4		304	0		0.2
5	8.9	110	13		283	0		0.2
6	9.2	102	10	0.8	283	0	70	0.2
7	9.8	105	12.6		283	0		0.2
8	8.6	102	20.6		253	0		0.2
9	9.4	106	18.4	6.0†	253‡	0	64	0.2
10					253‡	0		0.2
11	7.6	96	13		Lost	0		0.2
12	7.9	92	23.8	7.5†	113	0		0.2
13	6.2	85	33.6		513	0		
14	6.7	70	35.4	8.0	513		40	
19	3.8	50	27.6	4.0				
22	2.5	34	27				23	
25	2.4	32	22.7	0.8				
28				0.6				
30	3.7	47	16					
August 1					19			
2					19			
3					19			
4					22			
5					22			
6					22			
7					22			
8	4.8	70	15.6	0.6				

* S H (case 13) 47 Kg in weight and suffering from polycythemia vera, was treated with 0.2 Gm of phenylhydrazine hydrochloride daily from June 30 to July 13.

† Serum free from hemolysis.

‡ Bands of hematoporphyrin seen on examination of filtrate from stool.

§ Band reading equals approximate number of milligrams of urobilinogen daily.

globin and the number of red and white blood cells were followed. The urobilin was measured by the band method, and the figures given therefore, represent only approximately milligrams of urobilinogen. The details are given in table 9 and chart 6.

The initial excretion of urobilinogen was at a rather high normal level. Following the administration of daily doses of phenylhydrazine, there was an early decided fall in red blood cells and the percentage of hemoglobin and a simultaneous and considerable increase in the uro-

bilinogen content of the stool. Later, when the effect of the phenylhydrazine was more pronounced and a few days before the administration of the drug was discontinued, the serum bilirubin rose rather sharply and the patient became jaundiced. By this time the output of urobilinogen had become very great.

Unfortunately, it was impossible to measure the output of urobilinogen for two weeks after the drug was discontinued. On the day

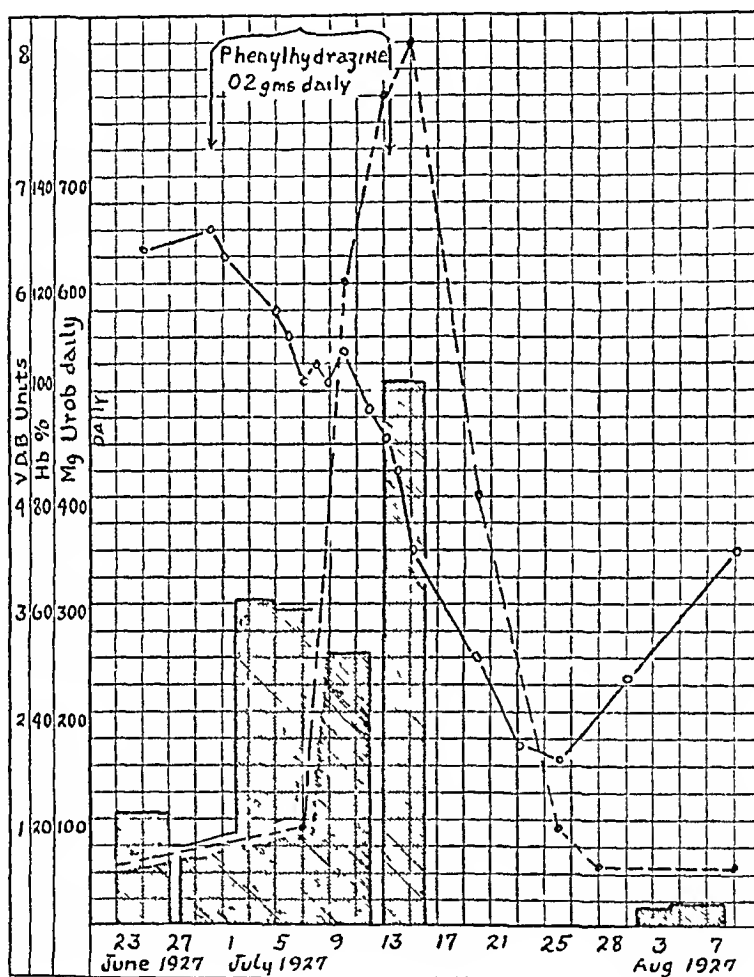


Chart 6—Results in a case of polycythemia vera in which phenylhydrazine was given (case 13, S H, showing initially hemoglobin 126 per cent, red blood cells 10,600,000 and white blood cells 14,800). The hematocrit reading was 73 per cent. In this chart the solid line indicates hemoglobin percentage, the broken line, as in the others, indicates serum bilirubin.

of the last dose the red blood cell count was 6,200,000 and the hemoglobin 85 per cent. Twelve days later the red blood count was 2,400,000 and the hemoglobin 32 per cent. By this time, however, jaundice had disappeared, the serum bilirubin was normal and it seemed that the effect of the phenylhydrazine was spent. Five days afterward, when estimations of urobilinogen were again undertaken, the hemoglobin and

red blood cell count were rising, serum bilirubin was normal and the excretion of urobilinogen was found to be much below its initial level. It is interesting that in the period before treatment and in the period of recovery there was some parallelism between the height of the red blood cell count and the level of excretion of urobilinogen. When the red blood cell count lay between 10,600,000 and 13,000,000, the output of urobilinogen averaged 92 mg per day. In the period of recovery, with the red blood count between 3,700,000 and 4,800,000, the daily average was 21 mg. A similar relationship between the hemoglobin percentage and the excretion of urobilinogen in dogs was noted by McMaster, Broun and Rous¹². Under the destroying influence of phenylhydrazine, the urobilinogen of the stool rose to at least 513 mg per day, an output fully as great as the excretion in cases of pernicious anemia in severe relapse. With the greatly increased blood destruction the patient became jaundiced and the van den Bergh reaction of the serum rose to 80 units. As was to be expected in jaundice due only to increased destruction of blood, the direct reaction was negative. It is noteworthy also that, in spite of a greatly increased blood destruction, urobilin was present in the urine in amounts insufficient to give a positive test by the zinc acetate or copper sulphate-chloroform methods.

Excretion of Urobilinogen in Malaria—In patients suffering from malaria with regular chills, it is usually considered that there is increased blood destruction.

CASE 14—A D., a man, aged 35, with dementia paralytica was admitted to the Toronto General Hospital in December, 1928, for malaria therapy. Although he was not robust in appearance there was no evidence of any other disease. In the control and incubation period the excretion of urobilinogen averaged 123 mg per day, a rather high level. When the fever rose and regular chills occurred, there was a prompt increase in the urobilinogen of the stool, which reached a maximum of 429 mg daily in a subsequent three day period. The serum bilirubin rose slightly. He became quite ill. The spleen and liver were enlarged and an appreciable amount of urobilin was found in the urine. The hemoglobin fell from 90 to 95 per cent to 78 per cent. The chills ceased spontaneously, the urobilinogen of the stool fell to a lower level, the serum bilirubin became normal, the urobilinuria ceased, the spleen and liver became smaller and the patient improved generally. The results are shown in table 10.

During the period of regular chills, estimation of the urobilinogen of the feces every day showed clearly, in spite of considerable irregularity in the size of the stool, that a huge increase in the output of urobilinogen occurred following each chill. Sometimes a small stool after

12 McMaster, P. D., Broun, G. O., and Rous, P. Studies of the Total Bile. I. The Effects of Operation, Exercise, Hot Weather, Relief of Obstruction, Inter-current Diseases, and Other Normal and Pathological Influences, *J. Exper. Med.* 37: 395, 1923.

the chill had a much greater urobilinogen content than a large stool on the next day. For instance, a 95 Gm stool for the day of a chill contained 872 mg of urobilinogen, while a 216 Gm stool on the subsequent day contained 84 mg. Often the increase in the urobilin output appeared in the stool that was passed the morning after the day of the chill.

Another patient given malaria therapy showed similar results although it was impossible to collect stools satisfactorily.

COMMENT

Relation of Destruction of Blood to Excretion of Urobilinogen—Although it appears that any increase in the destruction of the blood is

TABLE 10—*Observations in a Case of Dementia Paralytica in Which Malaria Therapy Was Given**

Date, 1928	Maximum Temperature of the Period	Hemo- globin, per Cent	Red Blood Cells, Millions	Uro- bilinogen in Feces, Mg per Day	Urobilin in Urine	Serum Bilirubin	Quinine Therapy, Grains Daily
December 9, 10, 11, 12	98.8	91		190	0	0.6	0
13, 14, 15	98.6	95	5.0	79	0		0
16, 17, 18	98.6	102		104	0		0
19, 20, 21, 22, 23	104.6			108	0	0.8	0
25, 26, 27, 28, 29	105	88	5.3	273	+	1.0	0
30, 31, January 1	103.4			310	+	1.0	0
1929							
January 2, 3, 4	104	78		420	trace	1.2	0
5, 6, 7, 8	102	77	4.5	200	trace	1.4	0
9, 10, 11	100.2	80		286	0		0
12, 13, 14	99	78		364	0	0.8	0
15, 16	98.6			220	0		30
17, 18, 19	99			148	0		15
20, 21, 22	98.6			156	0	0.6	15
23, 24, 25	98.6			216	0		15

* A. D. (case 14), weighing 68 kg., was inoculated with malaria infected blood on Dec. 17, 1928. The first chill occurred on December 21. Although the chills were dying off spontaneously, quinine therapy was begun on Jan. 15, 1929.

accompanied by an increased excretion of urobilinogen, it is improbable that all the hemoglobin destroyed can be accounted for as urobilinogen. In dogs, Broun, Rous and McMaster¹³ found that under ordinary conditions only a fraction of the estimated amount of destroyed hemoglobin was excreted as bilirubin. When blood destruction was increased, however, not only was there a great increase in the output of bilirubin but also a greater proportion of the hemoglobin lost could be accounted for as bilirubin.

There are further reasons for doubting the existence of a precise quantitative relationship between hemoglobin destroyed and urobilinogen.

¹³ Broun, G. O., Rous, P., and McMaster, P. D. The Relation Between Blood Destruction and the Output of Bile Pigment, *J. Exper. Med.* **37**: 733, 1923.

excreted Urobilinogen is a product of bacterial action, and it would be surprising if all the bilirubin excreted into the intestinal tract was converted quantitatively into urobilinogen. Constipation¹⁴ and other factors have been found to reduce the amount of urobilinogen in the stools. The most that can be claimed, therefore, at present, is that the urobilinogen excreted represents a large fraction of the hemoglobin destroyed.

However, McMaster and his associates¹⁵ have shown that urobilinogen in the stools is formed only from bilirubin excreted into the bowel, and that the amount of bilirubin excreted, independent of changes in diet, varies with the rate of blood destruction.

The great increase in excretion of urobilinogen accompanying known increase in destruction of blood is illustrated in the case of polycythemia in which phenylhydrazine was given and in the case of dementia paralytica in which malaria therapy was used. That such an increase occurs in hemolytic icterus has long been recognized. On the other hand, we know of no condition characterized by an increased excretion of urobilinogen in which it can be shown that increased destruction of blood does not occur.

The Hemoglobin Equivalent of Urobilinogen Excreted (a) *Normal*, (b) *Pernicious Anemia*—The average daily excretion in our controls was lower than that found by Lichtenstein and Terwen¹¹. Like them, we found great individual variation, but our average for ten cases is rather less than half the average value in their series of fifteen. The excretion of urobilinogen in pernicious anemia, however, was similar in both series, although one of their cases showed a greater output than any of ours.

(a) Assuming that the blood constitutes 5 per cent of the body weight, and that 4 Gm of urobilinogen is produced from 92 Gm of hemoglobin, Terwen⁶ calculated that one-one hundred and fortieth of the hemoglobin content of the blood in normal persons is excreted as urobilinogen every day. Calculating the rate for our controls in the same way, the daily normal excretion of urobilinogen is equivalent to about one-three hundred and fortieth of the blood hemoglobin, the maximum being one-one hundred and sixty-eighth.

(b) In cases of pernicious anemia, on the other hand, the relationship is very different. Assuming for purposes of calculation that the blood volume has the same proportion to body weight as in the normal condition, one finds that in patients with anemia of increasing severity

14 Elman, R., and McMaster, P. D. Studies on Urobilin Physiology and Pathology. II. Derivation of Urobilin, *J. Exper. Med.* **41** 513, 1925.

15 Rous, P., Broun, G. O., and McMaster, P. D. Studies on the Total Bile. II. The Relations of Carbohydrate to the Output of Bile Pigment, *J. Exper. Med.* **37** 421, 1923, footnote 13.

the hemoglobin equivalent of urobilinogen excreted each day becomes a larger and larger fraction of the calculated blood hemoglobin of the body until in patients in severe relapse it may amount to more than one tenth of this total. Immediately after the reticulocyte response the fraction becomes less than one-one hundredth, and thereafter remains within normal limits. This is shown by the data presented in table 11. The cases are arranged in order of severity of the anemia. These figures show that in pernicious anemia there is an inverse relationship between the rate of destruction of blood and the severity of the anemia, and that in all cases destruction of blood falls off markedly under treatment with liver.

TABLE 11—*The Value for the Fraction, Hemoglobin Equivalent of Average Daily Urobilinogen Excretion Calculated Total Blood Hemoglobin in Cases of Pernicious Anemia at Different Levels of Hemoglobin Percentage **

Case	Before Liver Therapy		Immediately After Reticulocyte Crisis		Late Observations Made			
	Hemoglobin Equivalent of Urobilin Excreted Daily		Days After Beginning Treatment	Hemoglobin Equivalent of Urobilin Excreted Daily		Months After Beginning Treatment	Hemoglobin Equivalent of Urobilin Excreted Daily	
	Hemo globin, per Cent	Total Blood Hemo globin		Hemo globin, per Cent	Total Blood Hemo globin		Hemo globin, per Cent	Total Blood Hemo globin
9 (H D)	78	1/80	13-27	80	1/143			
10 (J W)	70	1/74	11-19	86	1/290			
8 (H S)	62	1/55	23-37	84	1/121	6	80	1/200
12 (J R)	35	1/30	{17-25 25-39	40 60	1/50 1/133	5	90	1/318
5 (W C)	30	1/17	15-25	60	1/141			
2 (A G)	30	1/14	10-23	54	1/160	2	64	1/343
3 (A F)	29	1/13	11-17	55	1/106	3	70	1/109
7 (G D)	25	1/10	10-18	44	1/156			
1 (M G)	24	1/9	14-21	67	1/174			

* Only those cases in which Terwen's method was used are included

If pernicious anemia were primarily a hemolytic anemia, it might be expected that a considerable increase in the destruction of blood could be observed before there was any appreciable fall in the percentage of hemoglobin, and that the excretion of urobilinogen would be greatest when the hemolytic agent was acting on the largest number of red blood cells. It is found, instead, that the urobilinogen increases as the cells become more and more abnormal in appearance, and that usually it is greatest, absolutely and relatively, when the actual number of red blood cells is very low. When the hemoglobin is about 20 per cent, the excretion of urobilinogen is equivalent to one tenth or more of the calculated blood hemoglobin of the body.

Relation of the Number of Reticulocytes to the Increase in the Red Blood Cells—Minot, Cohn, Murphy and Lawson¹⁶ noted in cases showing a marked reticulocyte response that the increase in the red blood cells up to the time of the peak of the response was often approximately equal to the number of reticulocytes per cubic millimeter. In a subsequent paper¹⁷ it was remarked that such a relationship might be expected to exist "in so far as there has been no destruction of red blood cells, no change in distribution of body fluids, no maturation of reticulocytes to adult red blood cells, and no entrance into the circulation of nonreticulated erythrocytes." We found a similar relationship between the increase in red blood cells and the number of reticulocytes at or before the peak of the crisis in cases showing a very high reticulocyte response. Another explanation which takes into account the concomitant changes in the rate of destruction of blood is, however, possible. Before the commencement of liver therapy, the hyperplastic bone marrow produces large numbers of grossly abnormal cells—megalocytes, macrocytes, microcytes—that are rapidly destroyed. Following the ingestion of liver, the bone marrow is stimulated to supply, in addition to these abnormal cells, increasing numbers of immature (reticulated) red blood cells which have a longer expectancy of life. Equilibrium between the formation and the destruction of blood is maintained for a short time by the continued discharge of the abnormal cells into the blood stream, and the red blood count rises in virtue of the number of reticulocytes supplied. With the change in the character of blood formation in the bone marrow under the influence of liver therapy, more mature red blood cells, not so readily destroyed, enter the circulation. The reticulocytes of the circulating blood become mature, thereby reducing the proportion of reticulocytes in the blood smear to a normal number. The excessive excretion of urobilinogen ceases, and thenceforth the red blood count and hemoglobin rise gradually to normal.

Plasma Bilirubin in Pernicious Anemia, Its Relation to the Excretion of Urobilinogen—In most cases of pernicious anemia the plasma bilirubin is increased, but its actual level is by no means parallel either to the severity of the anemia or to the amount of urobilinogen excreted, although all three tend to vary in the same direction. In mild cases there is a considerable increase in the excretion of pigment without any significant rise in the bilirubin of the plasma. In severe cases the

16 Minot, G. R., Cohn, E. J., Murphy, W. P., and Lawson, H. A. Treatment of Pernicious Anemia with Liver Extract. Effects upon the Production of Immature and Mature Red Blood Cells, *Am J M Sc* **175** 599, 1928.

17 Cohn, E. J., Minot, G. R., Alles, G. A., and Salter, W. T. The Nature of the Material in Liver Effective in Pernicious Anaemia, *J Biol Chem* **77** 325 1928.

plasma bilirubin is always increased, but among several such patients excreting approximately equal amounts of urobilinogen there may be considerable variation in its level. The plasma bilirubin rises when the patient becomes worse and is usually highest in the patients that are critically ill. The highest value we have noted was 8.0 van den Bergh units in a patient just before his death (in 1925). In no case was a direct van den Bergh reaction observed.

The rapid decrease in plasma bilirubin shown in all cases during the reticulocyte response has been observed by Minot and Murphy¹ and others.

Urobilinuria in Pernicious Anemia—It has already been mentioned that urobilin can rarely be demonstrated in the urine in mild cases of pernicious anemia, and that it does not always appear in the urine in severe cases, even when the plasma bilirubin is high and when large amounts of urobilinogen are excreted in the feces. It is common to find small amounts of urobilin in the urine of patients in relapse, but strongly positive tests have been found only for patients that were seriously ill. In some instances patients were under observation while they became much worse; in these the transition was observed from negative tests or only traces of urobilin to such amounts that a positive test was obtained even when the urine was greatly diluted. In some instances there was an increase in the urobilinuria immediately after the beginning of liver therapy. In all cases, however, urobilin ceased to be demonstrable in the urine before the end of the reticulocyte response. It is probable that the increased urobilinuria in very ill patients is due, in part at least, to an associated disturbance in hepatic function.

The Cause of the Anemia—There have been many different opinions as to the cause of the anemia and the associated derangement of blood pigment metabolism in pernicious anemia, but for many years the dominant views have been (1) that it is primarily a disorder of blood formation, and (2) that it is due to hemolysis or increased blood destruction. Minot, Murphy and Stetson¹⁰ stated that they held to the conception of Pepper (1875) and Cohnheim (1876) that it is a disorder in the formation of blood. They have found it difficult to conceive that the prompt improvement following on liver therapy can be attributed to the arrest of a hemolytic process. Yet, they stated "that a dysfunction of haemoglobin metabolism, which may partly be due to abnormal red blood cell destruction is a feature of the disease." Whipple¹⁸ considered that

¹⁸ Whipple, G. H. Pigment Metabolism and Regeneration of Hemoglobin in the Body, *Arch Int Med* **29** 711 (April) 1922, *Experimental Anemias, Diet Factors and Related Pathologic Changes of Human Anemias*, *J A M A* **91** 863 (Sept 22) 1928.

the anemia of pernicious anemia is the result of a deficiency of stroma-building material or a disturbance of the stroma-building mechanism with an overproduction of pigment substances rather than an increased destruction of red blood cells. The tissues of the body, he contended, become saturated with pigment material produced in excess of the limited number of red blood cells, and this excess production leads to increased excretion of bilirubin and urobilin. Krumbhaar,¹⁹ on the other hand, while of the opinion that pernicious anemia is not primarily a hemolytic anemia, did not question the existence of increased destruction of blood in this disease. The excessive pigment metabolism, he wrote, is more likely a sign of increased blood destruction than of "elimination of hypothetical materials designed for haemoglobin formation but unavailable in the haemoglobin saturated state of the few functioning erythrocytes."

Peabody³ clearly demonstrated that the hyperplasia of the abnormal cells in unusual regions of the bone marrow disappears in the remission that results from liver therapy. The bone marrow, now apparently normal, once more supplies normal red blood cells to the circulating blood.

To us it seems most probable that the essential disorder in the anemia of Addison's "pernicious" anemia is one of formation of blood, but that there is a resultant secondary increase in its destruction. An abnormal bone marrow produces abnormal cells that are rapidly destroyed. With slight anemia and general macrocytosis, the excretion of urobilinogen is definitely but not markedly increased. In cases showing greater anisocytosis and more irregularity in form of the red cells, usually with moderate anemia, the output of the urobilinogen (i. e., destruction of blood) is greater. When the smear shows the characteristic picture of severe relapse, the excretion of urobilinogen is very great. Destruction of blood preponderates over its formation, and severe anemia results.

Following liver therapy, the bone marrow is stimulated to supply large numbers of immature but more normal red blood cells (reticulocytes) that have a long duration of life. The production of the grossly abnormal cells ceases and with their disappearance from the blood stream the excretion of urobilinogen falls off sharply. Adult erythrocytes more and more nearly normal in appearance, with a normal duration of life are now supplied. All signs of increased destruction of blood disappear. The red blood cell count and hemoglobin percentage rise and become normal. While the blood picture remains normal, the rate at which destruction of blood occurs also remains normal.

¹⁹ Krumbhaar E. B. Thoughts on the Morbid Processes Active in Pernicious Anaemia, *Am J M Sc* **175** 523, 1928

SUMMARY AND CONCLUSIONS

1 In patients with Addison's "pernicious" anemia in a state of relapse the excretion of urobilinogen is greatly increased and may be several times the normal value. In severe cases the amount excreted daily is equivalent to 8 to 13 Gm of hemoglobin, amounting in some instances to more than one tenth of the total blood hemoglobin of the body.

2 Following liver therapy and beginning at about the peak of the reticulocyte crisis, there is always a sharp decrease in the excretion of urobilinogen, which falls in a few days to a level within normal limits.

3 In cases of pernicious anemia showing little anemia, with general macrocytosis but little microcytosis or poikilocytosis, the excretion of urobilinogen is increased somewhat above a high normal value. With liver therapy the excretion of urobilinogen falls after a low reticulocyte response and is always normal when the blood picture has become normal.

4 The amount of plasma bilirubin in pernicious anemia varies in the same direction as the excretion of urobilinogen and opposite to that of the red blood cell count. It is highest in those patients who are critically ill. When it is high it falls to a normal level during the reticulocyte response.

5 In severe cases of pernicious anemia, urobilin is frequently found in the urine. Large amounts are present only when patients are very ill. Its excess then is attributable, in part at least, to altered liver function.

6 The disturbance in blood pigment metabolism in pernicious anemia is probably due to an abnormality of the red blood cells in virtue of which they suffer early destruction. The abnormal red blood corpuscles present in relapse are the ones most affected. Adequate liver treatment, promoting the production of normal red blood cells, retards the rate at which destruction of the blood occurs and allows the blood picture to become normal.

BRUCELLA INFECTION OF BRIEF DURATION

REPORT OF A CASE *

HUGH R LEAVELL, M D

MARY POSTON

AND

HAROLD L AMOSS, M D

DURHAM, N C

Undulant fever is generally considered to be a prolonged recurring disease Marston,¹ in 1881, reported the average duration to be from three to ten weeks, but recognized a form that he described as so mild that the patient may never be confined to bed and all the while may be supposed to be laboring under a peculiar form of dyspepsia He gave as diagnostic points in mild types of undulant fever (1) gastric derangement that refuses to yield to any treatment, (2) great depression of the spirits out of all proportion to the symptoms, (3) slight pyrexial attacks, and (4) anemia, slow and progressive, with a marked tendency to an attack of rheumatism or neuralgia In describing his own symptoms he probably described one of the earliest ambulatory cases

Hughes,² in his classic monograph published in 1897, disregarded doubtful and nonfatal cases of less than three weeks' duration Of three hundred and seventy-two cases that he studied, only 12 per cent lasted less than twenty days, and all of these were fatal In his series, the duration of 64.6 per cent of his cases was between thirty-one and ninety days

Basset-Smith,³ in 1903, gave three months as the minimum duration, though he stated that in Mediterranean countries the disease may terminate in from one to two months Eyre,⁴ who played a prominent part in the investigations made by the Mediterranean Fever Commission, stated that the duration of the disease is from six to nine months

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* From the Biological Division of the Medical Clinic of the Johns Hopkins University School of Medicine and Hospital

1 Marston, A J Report on Fever (Malta), Great Britain Army M Rep 3 507, 1881

2 Hughes, M L Mediterranean, Malta or Undulant Fever, London, The Macmillan Company, 1897

3 Basset-Smith, P W Duration of Mediterranean Fever, Brit M J 2 1589, 1903

4 Eyre J W H Milroy Lectures on Undulant Fever, Lancet 1 1747, 1908

There are certain types of cases that run a milder, and sometimes shorter, course than the average. In making studies for the Mediterranean Fever Commission, Shaw⁵ investigated a series of ambulatory cases of Malta fever. Samples of blood from five hundred and twenty-five dock hands in Malta were examined. Fifteen per cent of these specimens showed agglutination of *Brucella* in dilutions of 1:30 or more, with marked reactions in twenty-two cases. These cases were more thoroughly investigated. In all but three of them there was a history suggestive of mild febrile infection lasting from two days to three months. *Brucella* was recovered from the blood and the urine in three cases, from the blood alone in one case, and from the urine alone in six cases. All of the men studied were working at the time.

Cantani,⁶ in Naples, in 1908, described a benign type of Malta fever, discovered by studying the members of families in which more serious forms of the disease were being treated. In one family he noted five cases: one of extreme severity, three moderately severe and one mild. The last occurred in a boy, aged 11, who showed only fever, slight weakness and splenomegaly for a month. His blood serum agglutinated *Brucella* in dilutions up to 1:500. Cantani described thirteen cases of this type in other families. The disease in three of his cases, not bacteriologically proved to be cases of undulant fever, lasted only four days. He made the suggestion that the disease is by no means as malignant as is generally supposed, and that more intensive bacteriologic study of the milder cases would probably prove enlightening.

Cantaloube⁷ reported sixteen ambulatory cases in 1910, the majority of which were diagnosed by the agglutination reaction. The patients gave a history of several months' illness, with fever, perspiration, more or less generalized pain and constipation. Most of his patients had apparently been infected from eating unpasteurized cheese. He found that this type of infection sometimes persists as long as the more severe form, and that the slight fever may easily go unnoticed unless the temperature is taken systematically. Additional ambulatory and mild cases have been reported by Dargem and Dore⁸ and others.

The case to be described is an example of *Brucella* infection with fever of exceptionally short duration.

5 Shaw, E. A. The Ambulatory Type of Case in Mediterranean or Malta Fever, *J. Roy. Army M. Corps* **6**: 638, 1906.

6 Cantani, A. Sulle forme leggierissime di febbre di Malta, *Riforma med.* **24**: 365 (April 6) 1908.

7 Cantaloube, P. Les formes ambulatoires de la fièvre de Malte, *Echo med. de Cévennes, Nîmes* **11**: 22 (Feb.) 1910.

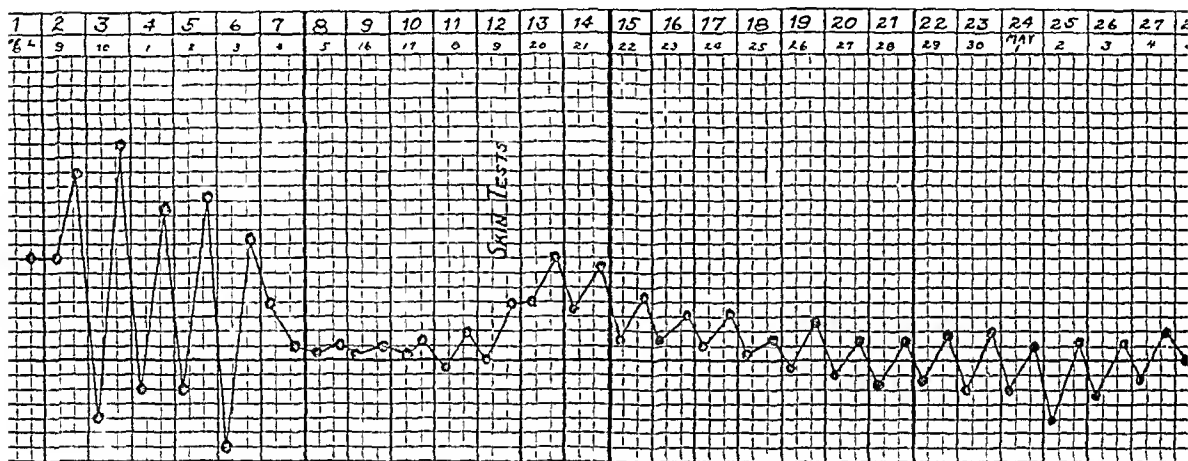
8 Dargem and Dore. Des formes frustes de la melitococcie, *Bull. et mém. Soc. de méd. d'hôp. de Paris* **49**: 122 (Jan. 23) 1925.

REPORT OF CASE

History—A 25 year old, unmarried physician was admitted to the Isolation Ward of Johns Hopkins Hospital on April 9, 1930, because of fever and general malaise of one day's duration

For fifteen years he had experienced attacks of migraine preceded by visual aura. During early childhood he had had measles, pertussis and varicella. His tonsils and adenoids had been removed several years prior to the present illness. No other facts of importance in his past history were elicited.

The day before admission he had rather suddenly been seized with headache, anorexia and general malaise, associated with constipation. He spent that afternoon in his room instead of going about his usual duties in the hospital. All of his symptoms became progressively worse, and by evening he noted the onset of aching pains throughout his body, more marked in the lumbar region and in the extremities. Later in the evening he felt worse and was quite prostrated, with increase in the headache and general pain.



The temperature in a case of undulant fever of brief duration. The numerals in the row at the top of the chart represent the days of the disease, those at the left, degrees Fahrenheit.

He had no rhinorrhea, chilliness, sore throat or cough. There were no symptoms referable to the genito-urinary tract.

Physical Examination—The temperature was 102.6 F, the pulse rate, 100, the respiration rate, 23, the blood pressure, 138 systolic and 72 diastolic. The patient looked ill and miserable, with flushed cheeks and suffused conjunctivae. The lower eyelids were puffy, but no edema was present elsewhere. No rose spots were found, and there was no rash, although a small aphthous ulcer was present on the buccal mucosa. The venules were dilated in the slightly reddened pharynx. Moderately enlarged lymph nodes were felt in the cervical, epitrochlear, axillary and inguinal regions, but only the right upper deep cervical node was tender. The heart showed no enlargement and was otherwise normal, with the exception of rare extrasystoles.

There was slight impairment of the percussion note over the apex of the left lung, but breath sounds and voice sounds were normal, and no râles were heard even after coughing. The liver was just palpable, but the spleen was not palpable until three days later. Some tenderness was noted over the tibiae, but it was not

marked. The reflexes were normal. At the time of admission influenza seemed the most likely diagnosis.

Laboratory Examination—The hemoglobin content (Sahli) was 98 per cent, the red blood cells numbered 4,790,000, the white blood cells, 6,760, polymorphonuclear neutrophils, 67 per cent, large lymphocytes, 12 per cent, small lymphocytes, 11 per cent, and large mononuclears, 10 per cent. There were no eosinophils.

The specific gravity of the urine was 1.008. There was a faint trace of albumin. No reducing substances were shown in the urine. The sediment showed red blood corpuscles, 3 per high power field, leukocytes, from 6 to 7 per high power field, and rare granular casts. There was a trace of urobilin. The result of a test for diacetic acid was mildly positive. No growth was obtained on culture of the urine.

In the culture from the throat there were a few beta-hemolytic streptococci, but no diphtheria bacilli.

The blood serum did not agglutinate typhoid or paratyphoid antigens. However, *Brucella* (less than one colony per cubic centimeter) was grown in a blood culture taken on the fourth day of the disease and planted on liver infusion agar of pH 6.6. The organisms grew as well aerobically as in 10 per cent carbon dioxide, were morphologically characteristic and did not ferment sugars. They agglutinated in serum prepared against a caprine strain of *Brucella* in dilutions up to 1:2,560, in serum prepared against bovine and porcine types in dilutions up to 1:1,280 and in the patient's own serum in dilutions up to 1:1,280.

By the ninth day, which was about the time the organisms recovered from the blood were identified as *Brucella*, the patient's serum agglutinated *Brucella* antigens as follows: a bovine strain in dilutions up to 1:1,280, caprine and porcine strains in dilutions up to 1:640. A blood culture taken at this time showed no growth.

Intradermal tests on the tenth day showed definite cutaneous hypersensitiveness to suspensions of *Brucella* and to extracts of *Brucella* prepared according to the methods of Ando⁹ and of Lancefield¹⁰ for isolating the specific soluble substance from bacterial bodies.

Six cultures made from stools collected from the eleventh to the thirtieth day after the onset according to the Amoss and Poston¹¹ technic did not show *Brucella*, and none was found in five cultures made from the urine.

The white count remained low, never rising to 7,000. On the fifth day, the spleen became palpable. A portable roentgenogram showed the lungs to be clear. Red blood corpuscles persisted in the urine for five days, then disappeared coincidentally with the disappearance of albumin. Nonprotein nitrogen was 26 mg per hundred cubic centimeters, and sodium chloride was 382 mg per hundred cubic centimeters of blood.

Course—The treatment was symptomatic, and after a week the patient's improvement was rapid. Although he was afebrile, with the exception of the

9 Ando, K. A Simple Method of Obtaining Soluble Specific Substances from Various Bacteria (*Streptococcus Viridans*, *B. Dysenteriae* and *B. Mallei*), *J. Immunol.* **17**: 555 (Dec.) 1929.

10 Lancefield, Rebecca C. The Antigenic Complex of *Streptococcus Hemolyticus*. I. Demonstration of a Type-Specific Substance in Extracts of *Streptococcus Hemolyticus*, *J. Exper. Med.* **47**: 91 (March) 1928.

11 Amoss, H. L., and Poston, M. A. Isolation of the *Brucella* Organism from the Stools, *J. A. M. A.* **93**: 170 (July 20) 1929.

mild reaction following the intradermal tests, the patient was kept in bed for four weeks. During the summer, he was somewhat weak, but was able to be up and to play golf from time to time. He was well in October, 1930, and on Feb 15, 1931, was examined by Dr Longcope, who found no abnormality.

Origin of Infection—The origin of his infection was not definitely determined, but the disease was probably contracted in the laboratory. As intern in the Isolation Ward, he had had contact with patients who had undulant fever, but not for two or three months prior to the onset of his own infection. And although he had not worked with *Brucella* in the laboratory for a similar period of time, he frequently visited there. It should be said, however, that no other cases or possible cases of infection with *Brucella* have occurred from this laboratory.

There had been no contact with animals, and the patient had consumed no unpasteurized dairy products.

Bacteriologic Results—*Brucella* recovered from the patient's blood has not been positively identified as to strain, but the luxuriance of growth even without carbon dioxide suggests the porcine type, as do the reactions to the differential dyes as described by Huddleson.¹² No inoculations of animals have been made.

COMMENT

A case of such short duration as the one reported is interesting from several points of view. The condition might easily have been mistaken for influenza had the blood culture not been taken. It seems possible that a good many cases of the type described pass for cases of some other condition. In several of the ambulatory cases described by Shaw and others there was a history of fever for a short period, and it is probable that a definite relationship exists between the ambulatory cases and those similar to the case under discussion.

It is important to consider patients with ambulatory and abortive cases as possible carriers of *Brucella*. The organism is known to persist in the stools and urine for considerable periods after the acute febrile stage has passed, and we recently¹³ reported a case in which *Brucella* was repeatedly cultured from the gallbladder, both on duodenal drainage and at operation. Our patient apparently did not become a carrier. But such a possibility in a mild case might well be of importance from the standpoint of public health. Since the disease does not seem to be highly communicable, the carrier problem need not be over-emphasized.

This case may also explain the cutaneous hypersensitiveness to *Brucella* and the presence of agglutinins for *Brucella* that have been described by many observers in patients with no history of undulant fever.

¹² Huddleson, I. F. The Differentiation of the Species of the Genus *Brucella*, Techn. Bull. 100, Michigan State Coll. Agric. Exper. Sta., August, 1929.

¹³ Leavell, H. R., and Amoss, H. L. *Brucella* Infection. Cultivation of *Brucella* from the Bile. Case Report, Am. J. M. Sc. **181**: 96, 1931.

SUMMARY

1 A case of *Brucella* infection with fever of seven days' duration is presented

2 The possible significance of cases of such short duration is discussed with regard to the possibility that the patients in whom they occur might subsequently become carriers, and with regard to the development of cutaneous hypersensitiveness to *Brucella* and of agglutinins for *Brucella* antigens

3 The difficulty of diagnosing such a case by ordinary clinical methods is pointed out

THE ENDERMIC REACTION IN BRUCELLA INFECTIONS *

HUGH R LEAVELL, M D

AND

HAROLD L AMOSS, M D

DURHAM, N C

The endermic reaction for *Brucella* infection has been used for the most part as a confirmatory test. But Burnet¹ and others have reported positive cutaneous reactions in cases in which the blood serum showed no agglutination with *Brucella* and in which the blood cultures were negative.

Various antigens have been used in testing for cutaneous hypersensitiveness to *Brucella* and its products. These antigens may be classified roughly into two groups: (1) bacterial suspensions and (2) filtrates of broth cultures.

The use of the filtrate of a broth culture from twenty to thirty days old was described in 1922 by Burnet,² who called the substance "melitin." It has since been widely used, particularly in countries bordering on the Mediterranean, and the results have varied. Tienti³ in 1923 reported specific reactions in nine cases of undulant fever, with negative results in forty controls. Olmer and Massot,⁴ Debre, Marie and Giroud,⁵ Lemierre, Marchal and Jaubert,⁶ Cazalas⁷ and Liege and Casteran⁸ reported about sixty additional cases of undulant fever in

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1 Burnet, E. Diagnosis of Mediterranean Fever by the Intradermal Reaction. Action of the Filtrate of Culture of *M. Melitensis*, Arch Inst Pasteur de l'Afrique du Nord **2** 187, 1922

2 Burnet, E. A New Method of Diagnosing Malta Fever, Compt rend Acad d sc **174** 421 (Feb 6) 1922

3 Tienti, E. The Value of the Intradermal Reaction in *Melitensis* Infections, Policlinico (sez prat) **32** 767 (June 1) 1925

4 Olmer, D, and Massot, M. On the Diagnosis of Malta Fever by the Intradermal Reaction, Marseille med **61** 1206 (Oct 25) 1924. Olmer, D. Burnet's Melitin, J med franç **18** 182 (May) 1929

5 Debre, R., Marie, J., and Giroud, P. Autochthonous Undulant Fever. Burnet's Melitin Test, Bull et mém Soc med d hôp de Paris **51** 1654, 1927

6 Lemierre, A., Marchal, C., and Jaubert, A. A Case of Autochthonous Undulant Fever, Diagnostic and Therapeutic Value of Burnet's Intradermal Reaction, Bull et mem Soc med d hôp de Paris **51** 1702 (Dec 29) 1927

7 Cazalas, X. A Case of Undulant Fever, Paris med **18** 161 (Aug 25) 1928

8 Liege, R., and Casteran, R. A New Case of Malta Fever Cured by a Single Injection of an Endoprotein Prepared from *B. Abortus Bang*, Gaz d hop **102** 41 (Jan 9) 1929

which specific reactions were obtained, using melitin. Their control groups, however, were small.

Schoenholz and Meyer⁹ used a product similar to melitin which they called "abortin," with apparently satisfactory results, as did Huddleson and Johnson¹⁰.

Another group of investigators has hesitated to accept the reaction to melitin as a specific reaction, but has acknowledged its possible usefulness. Biugi¹¹ reported positive results in 38 per cent of sixty control cases in which Burnet filtrate had been used. Tapia and del Valle¹² used both bacterial suspension and melitin. They observed positive reactions with both in seven of fourteen cases of undulant fever, with melitin alone in two, and with the suspension alone in five. They made seventy-one control injections. The filtrate gave false positive reactions in 25 per cent of these, the suspension gave such reactions in only 7 per cent. Sorge¹³ found positive reactions in 27 per cent of eighty-six controls with melitin. Agglutination of *Brucella* was negative in all but one of these positively reacting controls, and in that case it occurred only in the dilution of 1:80. More recently, Duffau¹⁴ obtained 16 per cent false positive reactions in seventy controls, both the filtrate and the suspension being used, but considered the reactions with the filtrate to be somewhat shapier.

Mitra¹⁵, Fornaco and Bua-Fazio,¹⁶ deFermo,¹⁷ Giordano¹⁸ and Simpson and Frazier¹⁹ found the bacterial suspension to be superior.

9 Schoenholz, P., and Meyer, K. F. The Purification of Abortin, *J Infect Dis* **40** 453 (March) 1927.

10 Huddleson, I. F., and Johnson, H. W. Brucellosis. The Significance of *Brucella* Agglutinins in the Blood of Veterinarians, *J A M A* **94** 1905 (June 14) 1930.

11 Biugi, A. The Burnet Intradermal Reaction in Malta Fever Infection, *Pensiero med* **13** 361 (July 20) 1924.

12 Tapia, M., and del Valle, A. Diagnostic Value of the Cutaneous Reaction with Specific Antigen in Malta Fever, *Med iberica* **22** 317 (Oct 13) 1928.

13 Sorge, G. The Value of the Intradermal Reaction in Malta Fever Infection of Children, *Riv di clin pediat* **23** 471 (July) 1925.

14 Duffau. The Utilization of the Laboratory in the Diagnosis of Undulant Fever, *Arch Inst Pasteur d'Algerie*, 1928, vol 6, no 4.

15 Mitra, M. The Intradermal Reaction in Mediterranean Fever of Infancy, *Pediatrics* **32** 721 (June 15) 1924.

16 Fornaco, L., and Bua-Fazio, F. The Intradermal Reaction for the Diagnosis of Malta Fever, *Riforma med* **40** 393 (April 28) 1924. Bua, F. Method and Value of Intradermal Reaction in Malta Fever, *Minerva med* **6** 394 (May 20) 1926.

17 de Fermo, C. Method and Value of the Intradermal Reaction in Malta Fever, *Gaz d osp, Turin* **48** 859 (Sept 11) 1927.

18 Giordano, A. S. *Brucella Abortus* Infection in Man. The Intradermal Reaction as an Aid in Diagnosis, *J A M A* **93** 1957 (Dec 21) 1929.

19 Simpson, W. M., and Frazier, E. Undulant Fever, Report of Sixty-Three Cases Occurring in and About Dayton, Ohio, *J A M A* **93** 1958 (Dec 21) 1929.

to the filtrate. In two hundred and sixty-nine controls, they found positive reactions in only a negligible percentage, although in cases of undulant fever they never failed to obtain strongly positive reactions.

All observers who have had any experience with the endermic reaction have reported a high percentage of positive results in cases of undulant fever, more or less regardless of the type of antigen used.

The specificity of the tests has been the subject of the greatest contention. The consensus seems to be that the bacterial suspension gives fewer false positive reactions than the filtrate. In fact, only a few false positive reactions with the suspension have been reported.

EXPERIMENTS

Intracutaneous tests were made in a small group of cases of undulant fever and in fifty-one controls. In addition to the antigens previously used, a saline extract was employed, prepared by shaking a suspension of *Brucella* in a shaking machine for forty-eight hours and then centrifugating it for one hour.

Attempts were made to isolate the so-called "specific soluble substance" according to the methods described for streptococci by Lancefield²⁰ and Ando.²¹

Bacterial suspensions were standardized by comparison of turbidity with the 1:1,000 United States Public Health silica standard and were heat killed. In the later tests, this standard suspension was diluted with saline solution 1:10 and 1:100, to decrease, if possible, the number of false positive reactions and to titrate the degree of cutaneous hypersensitiveness, as is done in the tuberculin reaction.

A relatively large number of different preparations made from several strains of *Brucella* were used in testing each case or control. For this reason, although the number of cases and controls is not great, a rather large number of injections were made—587 in all, an average of 9.6 in each person studied, and in none less than 6.

The reactions were read from eighteen to twenty-four hours after the injections, and classified, according to the size of the zones of erythema, as follows: reactions with zones of erythema measuring up to 0.7 cm, 0; from 0.8 to 0.9 cm, \pm ; from 1 to 1.4 cm, +; from 1.5 to 1.9 cm, ++; from 2 to 2.4 cm, +++; and 2.5 cm or more, ++++.

Although central necrosis resulted more frequently and was more marked in the cases of undulant fever, it was also present in the control group.

In classifying the results of endermic tests in any given case, the reactions to all the substances, rather than that to any one extract, used in that case, were considered.

A summary of the results is shown in table 1. The case of "possible undulant fever" occurred in a patient with a suggestive history, but

20 Lancefield, Rebecca C. The Antigenic Complex of *Streptococcus Hemolyticus*. I. Demonstration of a Type-Specific Substance in Extracts of *Streptococcus Hemolyticus*, *J. Exper. Med.* **47**: 91 (March) 1928.

21 Ando, K. A Simple Method of Obtaining Soluble Specific Substances from Various Bacteria (*Streptococcus Viridans*, *B. Dysenteriae*, and *B. Mallei*), *J. Immunol.* **17**: 555 (Dec.) 1929.

the cultures and the results of the tests for agglutinins in the blood serum were negative. All the other cases of undulant fever were proved bacteriologically to be definitely positive.

The group classified as "other unrelated diseases" was composed of cases of hypertension, arteriosclerosis, chronic arthritis (not apparently due to *Brucella*), duodenal ulcer, amebiasis, Hodgkin's disease, leukemia, aortic aneurysm, syphilis, lead poisoning, diabetes, abscess of the lung, meningitis due to *Streptococcus viridans*, erythremia,

TABLE 1—Results of Endemic Tests According to Diagnosis

Diagnosis	Cases	Reactions		
		Posi- tive, %	Question- able, %	Nega- tive, %
Undulant fever	9	78	22	0
Possible undulant fever	1*	100	0	0
Tuberculosis	6	33	66	0
Typhoid fever	2	0	50	50
Normal	12	25	33	42
Other unrelated diseases	31	18	38	44

* A physician who had lived in a Mediterranean country as a child and who in college had worked with fresh embryos from pigs.

TABLE 2—Results of Endemic Tests According to Preparation Used

Preparation	Cases	Reactions		
		Cor- rect, %	Question- able, %	False, %
Poreine suspension	63	57	18	25
1:100 dilution of poreine suspension	25	80	12	8
Poreine saline extract	36	80	14	6
Poreine Ando extract	13	54	31	15
Poreine Lancefield extract	13	54	23	23
Bovine suspension	62	45	20	35
Bovine saline extract	34	62	27	11
Bovine Ando extract	12	42	16	42
Bovine Lancefield extract	13	84		16
Caprine suspension	57	17	28	25
1:100 dilution of caprine suspension	25	92	4	4
Caprine saline extract	23	79	21	
Caprine Ando extract	13	80		20
Caprine Lancefield extract	13	61	23	16

bronchial asthma, cholecystitis and hyperthyroidism. No definite relationship could be found between the type of disease and the positive reaction in the control group.

Although twenty-two different preparations were studied, only fourteen were used in a sufficient number of cases to be tabulated. So many false positive reactions were obtained with filtrates of broth cultures that their use was abandoned early in the series.

The diluted saline suspensions and the saline extracts gave better results than the other preparations, the extracts prepared after the methods of Ando and of Lancefield gave somewhat better results than

the simple standard suspensions. It can be readily seen that none of the substances gave uniformly satisfactory results, and apparently a high percentage of correct reactions is the best that can be hoped for.

COMMENT

It is obviously of the greatest importance to evaluate the endermic test as a diagnostic measure. It is a procedure that is relatively simple and that requires little apparatus after the antigens are prepared. Therefore it is widely applicable even in isolated districts. However, the interpretation of the reactions is not uniformly simple, and unless certain precautions are used the results may be misleading.

The cutaneous hypersensitiveness observed by us in cases of undulant fever has varied from time to time in the course of the disease, and we are unable to lay down definite rules for this variation. Certain patients have been more reactive in the early stages of the disease, while of others the reverse has been true. Some persons have reacted more violently to certain strains of *Brucella* than to others, and the strain producing the most marked intracutaneous reaction has not always been of the same type as the one with which the patient was infected.

The injection of antigen for an endermic test brings with it the possibility of producing agglutinins that may complicate the diagnostic picture. This was described by Giordano and confirmed in the case of one of us, whose serum about six weeks after a series of endermic tests agglutinated *Brucella* in dilutions up to 1:1,280 although no agglutinins had been demonstrated previously.

The "erythema brucellum" described by Huddleson and Johnson,¹⁰ which occurred in veterinarians who had tended cows with contagious abortion is interesting in the study of cutaneous hypersensitiveness to *Brucella*. They described two types: one an urticaria-like lesion of short duration, the other a papular erythema lasting from three to four days. They found agglutinins with titers of 1:50 and 1:100 in the five men tested, who had manifested this erythema following the manual extraction of retained placentas in aborting cows. When endermic tests with *Brucella* filtrates were made, these men showed a prompt reaction, reaching a maximum in six hours. Other patients who had not shown the erythema, but who had had even higher titers of agglutination, showed a much less marked and more delayed cutaneous reaction to the filtrate. This is additional evidence that the cutaneous reaction may produce variable results in different persons.

CONCLUSIONS

1. The endermic reaction is of value in the diagnosis of undulant fever, particularly in cases in which no agglutinins for *Brucella* are

present in the blood serum and in which *Brucella* cannot be grown on culture of the blood, urine, stools or bile

2 The intracutaneous test is not definitely specific. Although the result is generally positive in undulant fever, it is not infrequently positive, or highly suggestive, in controls.

3 Representative strains of several different types of *Brucella* should be used in making the test. The interpretation of the test should be based on all the reactions rather than on a single one.

4 Extracts of *Brucella* prepared according to the methods of Lancefield and of Ando for securing the soluble specific substance gave no more specific results in our cases than did the simple saline suspensions and extracts.

5 It is probable that an extract of *Brucella* prepared by prolonged shaking of a saline suspension, followed by centrifugation to remove most of the organisms, gives fewer false reactions than other preparations. But such a preparation does not always give a positive reaction in undulant fever.

6 Heat-killed bacterial suspensions seem to have more specific action than bacterial filtrates.

7 It is of value to titrate the degree of the endemic reaction by using varying dilutions of suspensions of the strains being tested, as in the tuberculin reaction.

PEPTIC ULCER

ASSOCIATION WITH PULMONARY TUBERCULOSIS *

MILLS STURTEVANT, M D

AND

LOUIS LAWRENCE SHAPIRO, M D

NEW YORK

In 1926 we published a portion of a study of all the peptic ulcers recorded in 7,700 necropsy records in Bellevue Hospital¹. The part then published dealt with frequency, number, size, shape, location, color, sex and age. This article is a continuation of that study and will record the association of peptic ulcer with tuberculosis.

Fifteen years after Cruvelhier's original description of gastric ulcer, von Jaksch,² in 1844, reported that of his patients afflicted with gastric ulcer one-fifth were tuberculous. Dittich,³ the same year, mentioned a similar connection. Nine years later, Engel⁴ found 19 per cent. In 1864, Brinton⁵ quoted these figures but felt that the association of gastric ulcer with other diseases is "in proportion more akin to their known frequency, than to other of their circumstances". He pointed out that deaths from phthisis are rather more than 18 per cent of deaths from all diseases in persons over 20 years of age. Leube,⁶ in 1876, commented on this association and quoted von Jaksch, Dittich and the figures of Steiner, who found phthisis 33 times in a series of 110 necropsies in which open and healed gastric ulcers were found. He also quoted Wollmar who found in a series of 48 necropsies only 5 instances of phthisis. Leube thought that larger series should be studied and that the association of ulcer and tuberculosis was not proved. In 1894, Perry and Shaw⁷ published their much quoted study of the findings on

¹ Submitted for publication, Feb 23, 1931

* From the Department of Medicine, the University and Bellevue Hospital Medical College, New York University, and the Third Medical Division, Bellevue Hospital

1 Sturtevant, M., and Shapiro, L. L. Gastric and Duodenal Ulcers, Arch Int Med **38** 41 (July) 1926

2 von Jaksch. Beitrag zur Lehre vom perforierenden Magengeschwür, Prag Vierteljahrschr **3** 1, 1844

3 Dittich, in Papellier. Tuberculosis von Magengeschwür, 1854

4 Engel. Ueber Geschwüre, Schmidt's Jahrb **82** 237, 1854

5 Brinton, W. Lectures on Diseases of the Stomach, ed 2, London, 1864, p 155

6 Leube, W. O. Diseases of the Stomach, in Ziemssen. Cyclopaedia, 1878, vol 7

7 Perry, E. C., and Shaw, L. E. Guy's Hosp Rep **1** 171, 1894

duodenal ulcers in 17,652 necropsies. Among these they collected 70 cases of duodenal ulcers, 25 of which were associated with tuberculosis. Thus we have the pathologists noting the association of ulcer and tuberculosis, and the clinicians, for the most part, doubting any connection between these two disorders.

Fox⁸ remarked the absence of gastric ulcers in cases of tuberculosis that he had studied. Fenwick⁹ said that since 18 per cent of persons have tuberculosis, naturally 18 per cent of persons with gastric ulcers have tuberculosis. He found 9 cases of ulcer of the stomach in 1,000 autopsies on tuberculous patients and, using Welch's statistics that gastric ulcers occurs in 2 per cent of all diseases, he figured that ulcer is less common in tuberculosis than in other diseases. McFarland¹⁰ believed that the presence of peptic ulcers in the dead is usually quite independent of the disease from which the patient dies. Hauser¹¹ also doubted that tuberculosis has any special etiologic effect. Collinson and Stewart¹² felt that the theory of a tuberculous etiology has never received much support. They found 86 cases of tuberculosis in 1,000 unselected necropsies (8.6 per cent). In 151 necropsies on persons with peptic ulcers there were but 5 cases of tuberculosis (3.4 per cent) and when the series was extended to include ulcer scars, of the 282 cases there were but 8 associated with tuberculosis, reducing the percentage to 2.1. Lisa¹³ found 9 ulcers in 257 necropsies on tuberculous subjects and 4 ulcers in 209 nontuberculous patients. Emery and Monroe¹⁴ reported a clinical series from the Peter Bent Brigham Hospital. Of this series of patients 5.4 per cent suffered from pulmonary tuberculosis, 18 of the 30 cases were considered inactive tuberculosis. These authors thought that the tuberculosis did not influence the course of the ulcers and that there was no greater association of the two diseases than one would expect. In two books recently published in this country Rehfuß¹⁵ did

8 Fox, W. Diseases of the Lungs and Pleura. London, J. & A. Churchill, 1891, p. 606.

9 Fenwick, W. Soltan. The Dyspepsia of Phthisis. London, H. K. Lewis, 1894, p. 33.

10 McFarland, J. Surgical Pathology, Philadelphia, P. Blakiston's Son & Co., 1924, p. 564.

11 Hauser, G. Die peptischen Schädigungen des Magens des Duodenums und der Speiseröhre und des peptische postoperative Jejunalgeschwür, in Henke and Lubarsch. Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 4, p. 339.

12 Collinson, H., and Stewart, M. J. Chronic Peptic Ulcer of the Stomach with Acute Miliary Tuberculosis of the Gastric Mucosa, Brit. J. Surg. **15**: 626 (April) 1928.

13 Lisa, J. R. Surg., Gynec. & Obst. **41**: 664 (Nov.) 1925.

14 Emery, E. S., and Monroe, R. T. Peptic Ulcer, Arch. Int. Med. **43**: 846 (June) 1929.

15 Rehfuß, M. E. Diagnosis and Treatment of Diseases of the Stomach, Philadelphia, W. B. Saunders Company, 1927.

not mention this association, and Crohn¹⁶ said "A coincidence of the two conditions ulcer and phthisis is inevitable when one considers the wide incidence of both in the adult population"

Attempts to explain an association between peptic ulcer and tuberculosis are occasionally found Arloing¹⁷ suggested that the toxin of tuberculosis might be an etiologic factor in the production of ulcer of the stomach Kodon¹⁸ studied patients with ulcer, their mode of living and their family history He found tuberculosis in a severe form in the families of 49 patients afflicted with ulcer, and in 5 different families he found tuberculous lesions of the skin Kodon could not resist the thought that tuberculous infection must have some connection with round ulcer of the stomach Stiller¹⁹ believed that there is a connection, but thought that both conditions are the result of the asthenic constitution He found hyperacidity, chlorosis and atony of the stomach associated with tuberculosis and ulcer Meyer²⁰ approached the subject from still a different angle He pointed out the frequency of dyspeptic symptoms in the tuberculous and studied 50 cases of pulmonary tuberculosis with severe gastric symptoms Among these he found 4 definite and 2 suspected cases of duodenal ulcer He suggested that not only may tuberculosis predispose to peptic ulcer but that such ulcers, thus formed, are more likely to become chronic

Since sufficient evidence has been accumulated to make the coexistence of peptic ulcer and tuberculosis of a possible, if not indeed a probable, frequency beyond what one should reasonably expect even in two disorders so commonly found, we have thought it worth while to tabulate findings on this association in 7,700 necropsies at Bellevue Hospital and apply the ordinary statistical tests to the figures obtained The standard error has been figured after the formula $\sqrt{\frac{p \cdot q}{n}}$ in which p is a fraction whose numerator is the number of the sample showing deviation and whose denominator is the number of cases in the whole sample, q is the complement of that fraction and n is the number of cases in the sample The standard error of the difference of two rates is figured as the square root of the sums of the squares of the standard errors of the two rates

16 Crohn B B Affections of the Stomach, Philadelphia, W B Saunders Company, 1927

17 Arloing Des ulcerations tuberculeuses de l'estomac, Paris, Asselin & Honzeau, 1903

18 Kodon, E Ein Erklärungsversuch der Pathogenese des Ulcus rotundum-ventriculi Wien med Wchnschr 60 1992, 1910

19 Stiller, B Magengeschwür und Lungentuberkulose, Berl klin Wchnschr 48 325 (Feb 20) 1911

20 Meyer, J Peptic Ulcer Complicating Pulmonary Tuberculosis, Illinois M J 46 348 (Nov) 1924

Our study of 7,700 necropsies at Bellevue Hospital¹ showed the incidence of gastric ulcer and scars to be 120, and of duodenal ulcer and scars 44. There were 86 open gastric ulcers and 35 open duodenal ulcers. Deducting for open duodenal and gastric ulcers in the same person there were 117 cases of peptic ulcer.

Among the 7,700 necropsies studied, 891 patients were recorded as having active pulmonary tuberculosis, this is an incidence of 11.57 ± 0.36 per cent. Among the 120 patients with gastric ulcers and scars there were 43 who had suffered from active pulmonary tuberculosis at the time of death, an incidence of 35.83 ± 4.4 per cent. To be significant, the difference between the incidence of tuberculosis in the ulcer sample and in the whole sample must be over twice the standard error of the difference. The difference is 24.26 ± 4.4 per cent, which is, of course, highly significant.

Or if we reject the cases of healed ulcer as possibly misleading, in that these ulcers may have existed and healed before the onset of the tuberculosis we find that there were twenty-eight tuberculous subjects among the eighty-six with open ulcer. This is an incidence of 32.55 ± 5.05 per cent. The incidence of active tuberculosis in the whole sample is as already stated, 11.57 ± 0.36 per cent, so that here the difference is 20.98 ± 5.06 per cent, which is more than twice the standard error of the difference.

Of 44 patients showing at necropsy either healed or open duodenal ulcers, 10 had active tuberculosis. Two of these patients had tuberculous meningitis without discovered pulmonary tuberculosis. Disregarding the cases of meningitis, there were 8 tuberculous subjects in the group of 44, an incidence of 18.18 ± 5.8 per cent. The incidence of tuberculosis in 7,700 necropsies was 11.57 ± 0.36 per cent, and the difference was 6.61 ± 5.8 per cent which is far short of twice the standard error of the difference. We therefore feel that our duodenal ulcer sample is too small to be significant.

However if we combine the cases of unhealed duodenal ulcer and those of unhealed gastric ulcer found in the 7,700 necropsies, deducting for cases in which gastric and duodenal ulcers were coexistent, we have 117 cases of peptic ulcer. There were 33 instances of pulmonary tuberculosis in this sample, or 28.21 ± 4.1 per cent. The difference between the incidence of tuberculosis in the cases of peptic ulcer and in the whole sample studied would be 16.64 ± 4.1 per cent. This again is a marked difference, much more than twice its standard error.

Similarly if we compare the incidence of ulcer of the stomach in all necropsies, 86 in 7,700 (1.12 ± 0.12 per cent), with the incidence of ulcer of the stomach in the necropsies showing tuberculosis, 28 in 891 (3.14 ± 0.58 per cent), the difference is 2.02 ± 0.59 per cent, which is well over twice the standard error. Or if we compare the frequency of peptic ulcers in the whole sample 117 in 7,700 (1.52 ± 0.14 per cent),

with the frequency in the tuberculous group 33 in 891 (37 ± 0.63 per cent), we have a difference of 2.18 ± 0.64 per cent

Further striking association is shown in other groups of pulmonary and pleural diseases. Thirty patients described as having chronic adhesive pleurisy were among the eighty-six with open gastric ulcers. Thirteen of these, however, were patients having active pulmonary tuberculosis, and of the remainder a certain number were undoubtedly tuberculous.

Pneumonia has been mentioned as associated with ulcers.² Nine cases of lobar pneumonia were found among the eighty-six patients with open ulcers who were not suffering from active tuberculosis. Likewise eleven patients with neither tuberculosis nor lobar pneumonia had bronchopneumonia. The bronchopneumonia was, for the most part, a terminal condition complicating disease of the kidney or heart or other illnesses that might predispose to ulcer. It is difficult to see how lobar pneumonia, a disease of comparatively short duration, could have had anything to do with the pathogenesis of chronic ulcers of long standing. It is possible that ulcers may predispose to pneumonia or that they are, for similar or different reasons, to be found in a particular constitutional pattern.

Bronchitis and emphysema were also frequently mentioned in association with peptic ulcers. It was impossible to separate a bronchitis or emphysema group of such purity and size as to be significant. These associations were striking enough, however, to suggest that some common factor in pulmonary disease might predispose to ulcers or that ulcers might predispose to pulmonary disease. An example of a common factor in pulmonary disease would be cough. It is known that vomiting is a cause of gastric erosions.²¹ Cough is similar physiologically, is accompanied by marked alterations in intra-abdominal pressure and may be accompanied by vomiting, if severe and prolonged. A possible mechanism for ulcer as an incident in pulmonary disease is suggested by the early exaggerated parasympathetic tonus seen in tuberculous disease.²² Constitutional predisposition to diseases that are themselves otherwise unrelated is possible.

SUMMARY

A review of the literature of the association between peptic ulcers and tuberculosis is given, showing great difference of opinion. Figures obtained from a study of 7,700 necropsies at Bellevue Hospital are presented, which reveal a definitely increased frequency of peptic ulcers in tuberculosis. This frequency is shown to be statistically sound.

21 Aschoff, L. Lectures on Pathology, New York, Paul B. Hoeber Inc., 1924, p. 290.

22 Kuntz, A. The Autonomic Nervous System, Philadelphia, Lea & Febiger, 1929.

CONGESTIVE HEART FAILURE

XI THE EFFECT OF DIGITALIS ON THE DYSPNEA AND ON THE VENTILATION OF AMBULATORY PATIENTS WITH REGULAR CARDIAC RHYTHM [†]

T R HARRISON, M D

J ALFRED CAIHOUN, M D

AND

F C TURLEY, M D

NASHVILLE, TENN

Digitalis has been used in the treatment of cardiac disease for nearly a century and a half, but there is still no general agreement as to when it should be given. Although a complete review of the literature will not be attempted, the following brief résumé will suffice to illustrate some of the disputed points. For the sake of clarity it should be stated here that the term "regular rhythm" as used in this paper includes persons who have sino-auricular rhythm either with or without premature beats.

1 *Is digitalis of value in auricular fibrillation?* All authors agree on an affirmative answer.

2 *Is digitalis ever of value in patients with regular rhythm?* Sir James Mackenzie (1920) believed that the drug was of little value except in patients with auricular fibrillation. Later (1925), however, he stated, in speaking of cardiac failure without valvular disease and with regular rhythm: "Without why or wherefore, drugs of the digitalis group occasionally have a good effect." Vaquez (1924) believed that while digitalis is of great value in auricular fibrillation, its value is much less than that of strophanthus in patients with regular rhythm. He thought that although digitalis acts as well as or better than strophanthus on the auriculoventricular node, the latter drug had a much greater tonic effect on the heart and hence was much better in patients with paroxysmal dyspnea.

On the other hand, Christian (1918, 1919, 1925) insisted that digitalis is of great value in patients with regular rhythm. Most authors agree with this opinion to the extent of believing that the drug is bene-

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* From the Department of Medicine of the Vanderbilt University Medical School.

ficial under certain conditions in such patients (Rosenbach [1897], Broadbent [1900], Cushny [1911], Cohn [1915], Osler [1919], Piatt and West [1920])

3 *Is digitalis of value in patients with regular rhythm and with edema (right ventricular failure)?* Mackenzie (1920) claimed that such benefit as was observed was due to a diuretic action, and this appears to have been Withering's view. Most other authors, however, believe that the beneficial diuretic action in such cases is secondary to the drug's effect on the heart. In summarizing opinions in this matter Robinson (1923) stated "There is general agreement that in cases of myocardial insufficiency with edema, diuresis follows the administration of digitalis, the edema is diminished or disappears and there is general improvement in symptoms." In his well controlled study, Marvin (1927) pointed out that in cases with regular rhythm and edema, digitalis is most effective in subjects with arteriosclerotic heart disease and least effective in patients with rheumatic disease, persons with syphilitic disease being intermediate in this respect.

4 *Is digitalis of value in patients with regular rhythm without edema and with cardiac asthma (left ventricular failure)?* Concerning this point many authors make no positive statements. The reason for lack of certainty in this regard probably is the fact that, while changes in the urine volume and the body weight allow one to make a decision based on quantitative determinations of the effect of a given measure on the degree of edema, conclusions in regard to dyspnea, which is a subjective phenomenon, are attended with more difficulty.

Many authors advocate giving digitalis whenever there is a "break in compensation," but, as they do not define the term, one is left in doubt as to whether or not they consider paroxysmal dyspnea as an indication for the drug. However, some authors are more specific. Rosenbach claimed that digitalis was of value in cardiac asthma. Broadbent, Hirschfelder (1913) and Osler insisted on the value of digitalis in cases of left as well as right ventricular failure. On the other hand, Vaquez stated that digitalis is far inferior to ouabain in this regard. Cohn, Robinson and Gibson (1927) stated that the effects of the drug are less beneficial in patients without edema than in those with edema. Mackenzie at one time denied, but later affirmed, the value of the drug in the cases under discussion.

5 *Is digitalis of value in patients with diminished cardiac reserve but without congestive failure?* (We use the phrase "diminished cardiac reserve but without congestive failure" to indicate the state in which a patient has no discomfort at rest—no orthopnea, paroxysmal dyspnea or edema—but experiences dyspnea on the performance of an exertion

which he could previously do with ease) In patients who, having had congestive failure, regain compensation, Eggleston (1925) and Christian (1925) advocated the continued use of small doses of the drug Probably most cardiologists in America at least, agree with this view But when is one to start digitalis in a patient who has never had symptoms at rest but who is beginning to have dyspnea with exercise? Christian (1925) stated that the drug is usually contraindicated when symptoms are slight or absent, but should be given if symptoms are increasing in severity Neither Osler, Robinson nor Cohn apparently believed in giving the drug until decompensation supervened Hirschfelder thought that digitalis should be given whenever there was dilatation, regardless of whether or not signs of decompensation were present Cushny (1925) stated

It is difficult to determine at what stage of insufficiency digitalis treatment should be commenced It is obviously unnecessary in the slighter forms such as are indicated by some breathlessness after exertion, which is so common in advancing years At the same time there should be no hesitancy in prescribing it when the circulation is more distinctly strained Small doses may be tried without any apprehension that they may induce unpleasant symptoms, and no tolerance is acquired in practice, so that its early exhibition does not prejudice its use when advance in the insufficiency demands treatment more imperatively At present this use of digitalis must be regarded as merely tentative until the indications for its use are more definitely determined

As a result of their demonstration that digitalis caused a diminution in the output of the heart in dogs, Harrison and Leonard (1926) believed that the drug might be of value in preventing, as well as in combating, congestive failure

6 Is digitalis of value in patients with cardiac disease without diminution of cardiac reserve, i e, without symptoms? There seems to be agreement by all authors that the drug is not indicated under such conditions

One may summarize the foregoing review by saying that there is universal agreement concerning the benefit to be derived from digitalis in patients with auricular fibrillation, and almost as great unanimity in regard to its value in many cases with regular rhythm and edema, but that there is considerable diversity of opinion concerning its effect in patients with paroxysmal dyspnea and in regard to the question of when if at all, it should be administered to patients whose only cardiac symptom is dyspnea on exertion The present study was undertaken in an endeavor to elucidate the unsettled problems just mentioned Interest has been particularly centered on the effect of digitalis in patients with paroxysmal dyspnea

METHOD

All patients were ambulatory. Subjects with more than slight edema and subjects with cardiac neurosis were excluded from the series. In all cases there was demonstrable cardiac enlargement. The majority of the patients had hypertension, arteriosclerosis or syphilitic aortitis as the cause of their cardiac disorders. There were only two cases of rheumatic disease. In three patients the underlying cause could not be determined and such cases were classified simply as cardiac enlargement. Several patients had two or more possible etiologic factors and were classified according to which factor seemed most important.

Dyspnea was present in every patient, and was usually the chief and sometimes the only symptom. In twenty-four cases, dyspnea with exertion only was complained of, whereas nineteen patients, in addition to having dyspnea with exercise, also had paroxysmal attacks of shortness of breath, usually at night. At each visit a record was made of the frequency and duration of such attacks.

The desired plan consisted in prescribing digitalis without instituting any other therapeutic measure whatever, without changing the patient's activities, without limiting fluids, without altering his diet and without prescribing sedatives. This plan was not strictly adhered to, as the patient's symptoms sometimes demanded other therapy, but in thirty-eight of the forty-three patients no therapy other than digitalis was given. The drug was administered in the form of capsules or tablets of the powdered leaf. The most frequent dosage was 0.6 Gm daily for three days and then 0.2 Gm daily for an indefinite period. In several cases the initial dose was 1 Gm daily for two days, and in one instance the patient was given 2 Gm at a single dose. The general plan was to give from 1.5 to 2 Gm in the first three days and from 2.5 to 3 Gm in the first week. No serious toxic symptoms resulted in any case, although nausea occurred occasionally and vomiting rarely. Electrocardiograms were made in some patients but not in all of them. As our interest was in subjective rather than objective phenomena, no attempt was made to control our therapy by frequent electrocardiograms. Teleoroentgenograms were made in all cases in which the question of the presence or absence of cardiac enlargement could not be definitely answered by physical examination. The majority of the patients were seen in the medical outpatient department of the Vanderbilt University Hospital, but a few patients treated by one of us in private practice are included. Most of the patients included in the series were followed from three to six months. A few patients were observed for periods of several weeks only, and a few of them have been followed for two years or more. In going over the records we have attempted to be conservative in ascribing improvement to digitalis. When there was

any reasonable doubt from the patient's statements as to whether he was benefited we have regarded the condition as unimproved. Two of us tabulated the results separately, the data were then combined and for each patient the tabulation which showed the least improvement was adopted. It is obvious that when a patient states that a given symptom has disappeared the chances for error are slight, whereas when he states that the symptom is better but still present, the chances for error are greater.

The term "paroxysmal nocturnal dyspnea" as used in this paper refers to attacks of shortness of breath which wake the patient up, and is not to be confused with orthopnea, an allied but not identical symptom.

It soon became obvious from the records of the patients' symptoms that the effect of digitalis in patients with paroxysmal dyspnea was so striking as to leave little question as to its value. In patients with dyspnea on exertion only, the results were much less dramatic and, although many patients seemed to think they were benefited, we were in doubt as to how much of this subjective improvement was real and how much was imaginary. Consequently, it seemed necessary to devise some means of achieving a quantitative expression of dyspnea.

Such a method was developed and has been described in the preceding paper in this series. This method consisted, in brief, of measuring the vital capacity and the ventilation during and after a series of carefully standardized exercises. The ventilation was divided by the vital capacity and multiplied by a correction factor for the body weight. The figure arrived at in this way was called the ventilation index. In order to determine objectively whether digitalis actually does cause improvement in dyspnea on exertion, respiratory measurements were made in eight patients before and after digitalis was given.

RESULTS

The Effect of Digitalis on Paroxysmal Nocturnal Dyspnea—The reports of the subjective conditions of nineteen subjects with this symptom are shown in table 1. One patient was worse after digitalis, two subjects were better and sixteen of the nineteen persons were entirely relieved. The effect was often dramatic, occasionally almost magical. A patient who had not slept for days except for intermittent nodding while sitting upright would report complete relief within two or three days after the drug was begun. Most patients noted some improvement within twenty-four hours, but in several instances the maximum result was not reached for a week or more. In many cases the benefit from digitalis was almost comparable to that from insulin in diabetic coma.

The length of time during which the drug was effective was not studied carefully in this series of cases, as many of the patients made only a few visits to the clinic. However, several patients have been followed for more than two years without any recurrence of paroxysmal dyspnea being noted. In other cases the symptoms have recurred despite digitalization.

The Effect of Digitalis on Dyspnea Brought on by Exertion—Forty-three patients were studied and the findings are presented in table 2. Two patients reported that they had more dyspnea after

TABLE 1—*The Effect of Digitalis on Paroxysmal Nocturnal Dyspnea*

Subject	Chief Diagnosis	Degree of Paroxysmal Dyspnea		Degree of Relief
		Before Digitalis	After Digitalis	
H O	Hypertension	+	0	Complete
D S	Hypertension	+	0	Complete
L C	Hypertension	++	0	Complete
M G	Hypertension	+++	0	Complete
A C	Hypertension	+	0	Complete
H M	Hypertension	++	0	Complete
J P W	Hypertension	++	0	Complete
A A	Hypertension	++	+	Partial
W T	Hypertension	++	+++	Worse
H Ma	Hypertension	++	0	Complete
A Is	Arteriosclerosis	++	+	Partial
R O E	Arteriosclerosis	+	0	Complete
E C	Arteriosclerosis	+	0	Complete
P A	Arteriosclerosis	+-	0	Complete
D K	Arteriosclerosis	+++	0	Complete
C C	Syphilitic aortitis	+++	0	Complete
F D	Syphilitic aortitis	++	0	Complete
S R	Mitral stenosis	+	0	Complete
A C	Cardiac hypertrophy	+	0	Complete

having digitalis. Twelve patients noticed no difference. Fourteen patients felt certain that they could perform the same exercise with less discomfort, and fifteen patients reported no dyspnea after digitalis. (The term "no dyspnea" does not mean that severe exercise would not have produced respiratory discomfort but simply that the amount of exertion involved in the patient's daily life caused none.)

It is certain that the results were much less striking as regards dyspnea with exertion than as regards paroxysmal dyspnea. The latter symptom was relieved completely in approximately 85 per cent of the cases, whereas the former symptom was entirely abolished in only about 35 per cent. Although an additional third of the patients claimed to be benefited, it is difficult to evaluate their statements. Disappearance of a symptom is decidedly more convincing than mere improvement in it.

The Effect of Digitalis on the Ventilation Index—As has been stated, it was our clinical impression that respiratory distress on exertion was often benefited by digitalis. However, the results were not

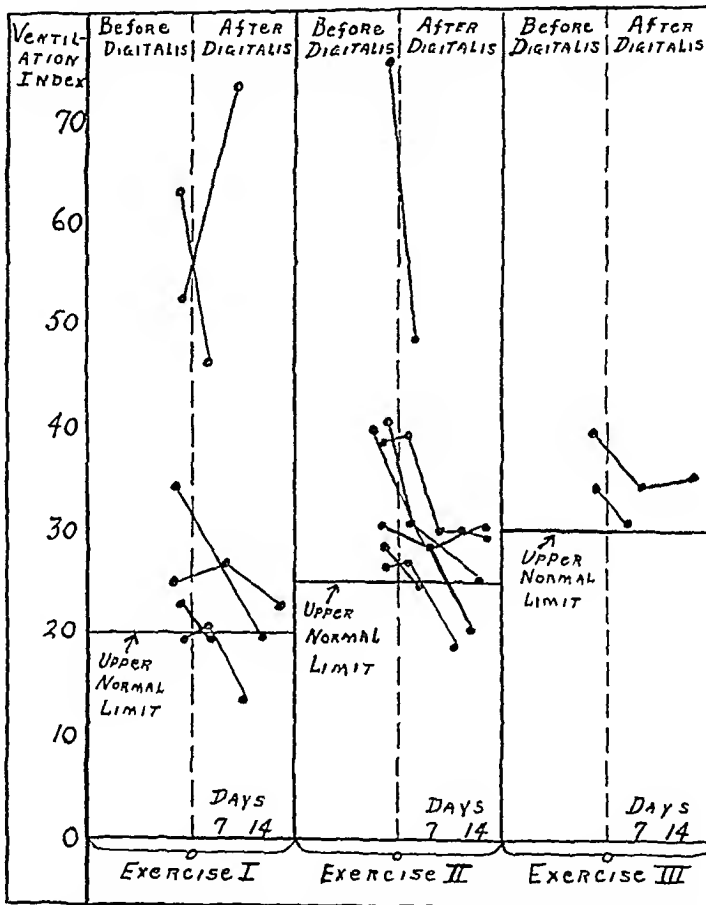
TABLE 2—*The Effect of Digitalis on Dyspnea Brought on by Exertion*

Subject	Chief Diagnosis	Degree of Paroxysmal Dyspnea		Degree of Relief
		Before Digitalis	After Digitalis	
H O	Hypertension	+	+	None
D S	Hypertension	+	+	None
L C	Hypertension	++	0	Complete
M G	Hypertension	++	+	Partial
A C	Hypertension	+	0	Complete
H M	Hypertension	++	+	Partial
J P W	Hypertension	+	0	Complete
A A	Hypertension	++	+	Partial
W T	Hypertension	++	+++	Worse
H Ma	Hypertension	++	+	Partial
A As	Arteriosclerosis	++	++	None
R O F	Arteriosclerosis	++	+	Partial
E C	Arteriosclerosis	+++	++	Partial
P N	Arteriosclerosis	++	+	Partial
D K	Arteriosclerosis	++	0	Complete
C C	Syphilitic aortitis	++	++	None
F D	Syphilitic aortitis	+++	+	Partial
S R	Mitral stenosis	+	0	Complete
A C	Cardiac hypertrophy	++	+	Partial
A H	Hypertension	++	+	Partial
J W K	Hypertension	++	0	Complete
J R	Hypertension	+	+	None
E E	Hypertension	+	+	None
W N B	Hypertension	+	+	None
S W	Hypertension	++	++	None
B S	Hypertension	+	++	Worse
J S	Cardiac hypertrophy	++	0	Complete
L O	Hypertension	+	0	Complete
M E J	Hypertension	++	+	Partial
M C	Hypertension	+	+	None
L B	Hypertension	++	++	None
D T	Hypertension	++	0	Complete
P A M	Hypertension	++	0	Complete
J V	Arteriosclerosis	++	+	Partial
T B H	Syphilitic aortitis	++	0	Complete
J P	Syphilitic aortitis	+	+	None
L V	Syphilitic aortitis	++	0	Complete
C H	Syphilitic aortitis	++	0	Complete
M B	Cardiac hypertrophy	++	+	Partial
W K	Chronic bronchitis	++	+	Partial
R L	Asthma	+	+	None
M L S	Cardiac hypertrophy	+	0	Complete
J A	Hypertension	++	0	Complete

nearly so striking in this instance as they were in regard to paroxysmal nocturnal dyspnea, and even though we attempted to be very conservative in our reports, and to make allowance for the enthusiasm which many patients have over any new therapeutic measure, it was believed that the observations of the clinical states did not justify any definite

conclusions as to the value of the drug in these relatively early cases. For this reason an attempt was made to study the matter more exactly by means of the vital capacity, the ventilation per square meter and the ventilation index.

Observations on eight cases are shown in the accompanying chart. None of these patients had edema at the time they were studied, and none had even had more than the slightest pitting. Four of them had had paroxysmal dyspnea before digitalis was administered, and in three



It can be seen that the ventilation index was usually less after digitalis had been given. In several instances the diminution did not come until the patient had been taking the drug for several days. In only one subject was there a marked increase in the ventilation index after digitalis had been administered.

Of the four this symptom disappeared soon after the drug was given. The fourth patient (W T) was not improved. All eight patients had dyspnea on exertion and four of them believed themselves much better in this regard after digitalis. Three of the others thought that their discomfort with exertion was less but did not seem certain. The eighth patient (W T) said that he was more short of breath on walking after digitalis and seemed to be so when he performed the test.

In the twenty-five determinations of the ventilation index after digitalis had been administered, a large reduction was observed thirteen times, a slight reduction six times, a slight increase (usually very slight) five times and a marked increase once (W T) Seven of the eight patients had, on the average, a lower ventilation index after the drug In two patients, tests done after digitalis had been administered for two or three days only showed no change, but later tests showed a well marked decrease in the ventilation index

The objection might be raised that since the observations after digitalis were made subsequent to those before the drug, the lower values were due not to the drug but to the fact that the patient had become used to the test and better trained to the exercise This objection is not valid because almost every person is "trained" to climb stairs and also because it was shown in the previous paper of the series (Harrison, Turley, Jones and Calhoun [1930]) that initial values are not higher than those obtained on subsequent tests

It is of some interest to note that before digitalis was given, the ventilation index was above the upper normal limit for the corresponding exercise in every patient (R O E had a ventilation index of 19.9 for exercise I, the upper normal limit being 20, but for exercise II, his ventilation index was 26.5, the upper normal limit being 25.0) After digitalis, four of the eight patients had ventilation indexes at or below the upper normal limit, although only one of these (R O E) was as low as the normal average

COMMENT

Since both subjective and objective data were in agreement, the conclusion seems justified that digitalis is usually of value in patients with regular cardiac rhythm suffering from paroxysmal nocturnal dyspnea or from dyspnea on exertion (provided, of course, that the dyspnea is due to disease of the heart) The number of our patients with rheumatic heart disease was too small to justify generalizations in regard to this condition, but patients with hypertensive, arteriosclerotic and syphilitic heart disease were usually benefited So far as we know, the present data constitute the first objective demonstration of the value of digitalis in benefiting the dyspnea of patients with regular rhythm without frank congestive failure, although Cohn and Stewart (1924) have demonstrated objective effects of the drug in such patients with congestive failure

The observations concerning the ventilation index seem to indicate that this method of study may be of some general use in evaluating therapeutic measures in patients with cardiac disease Until the present time it has been easy to determine whether a given drug was of value in combating cardiac edema, because the urine volume could be measured

and the patient could be weighed. Methods of expressing dyspnea quantitatively have not been available and this probably explains the general confusion which, as has been pointed out, has existed in regard to the value of digitalis at an early stage when the patient has dyspnea only.

Although the data reported indicate clearly that digitalis is of value in patients with cardiac disease and regular rhythm, they do not throw any light on the mechanism whereby the drug produced improvement except so far as they demonstrate improvement without changes in heart rate and without diuresis.

Heymans and Heymans (1926) have demonstrated the existence of respiratory reflexes arising from the heart and aorta. Recently, Sutton and Lueth (1930) have shown that acute mechanical distention of the aorta and of the left ventricle produces paroxysmal dyspnea in the dog. It is possible that reflexes from the heart may play some rôle in the production of paroxysmal dyspnea in man. If cardiac dilatation per se can produce dyspnea, one would expect digitalis to have a very beneficial action. However, the fact that the drug has such an effect in striking degree can in no sense be regarded as proof that the dyspnea is due to dilatation. Further data along this line are needed.

SUMMARY

The effect of digitalis has been studied in forty-three patients with regular cardiac rhythm. Most of the patients had never had congestive failure. None of them had more than slight edema at the time they were studied and the majority had none. The following results were obtained:

- 1 Nineteen patients had paroxysmal nocturnal dyspnea (cardiac asthma). Sixteen of these persons were completely relieved of this symptom by digitalis, two patients were partially relieved and one was worse after the drug.

- 2 Forty-three patients had dyspnea brought on by exertion. Definite benefit was obtained in fifteen of these, apparent benefit in fourteen and no improvement in twelve, and two patients were worse after the drug.

- 3 In eight subjects the vital capacity, ventilation per square meter on standardized exercise and ventilation index were studied. Seven of the eight patients reported clinical improvement of some degree and in all of them measurements of ventilation also indicated improvement. One patient felt worse after digitalis, and objective study of the ventilation showed that he was worse.

As a result of this study, it is concluded that digitalis is of great benefit in patients with paroxysmal dyspnea and is of some value in many patients with dyspnea brought on by exertion.

ILLUSTRATIVE CASES

CASE 1—H O, the patient, a Negress, aged 41, complained of mild smothering spells on lying down, and of slight shortness of breath on exertion, her ankles occasionally were slightly swollen

Physical examination revealed slight cardiac enlargement, the pulmonic second sound was exaggerated and there was a soft systolic murmur at the pulmonic area. The pulse was regular, the blood pressure was 148 systolic and 100 diastolic, the Wassermann reaction was negative. Teleoroentgenograms showed that the heart was at the upper limit of normal size.

She was put on potassium iodide, and two weeks later her dyspnea was unimproved. Digitalis was then given, 1 Gm daily for two days and 0.1 Gm daily thereafter. Four days later she reported no nocturnal dyspnea or orthopnea. Two weeks after this there was still no orthopnea and the patient believed that her dyspnea on exertion was better.

CASE 2—D S, the patient, a Negress, aged 39, complained of slight dyspnea on exertion for several months, for one month she had had mild paroxysms of dyspnea at night. There had never been any edema.

Physical examination revealed slight cardiac enlargement. The blood pressure was 162 systolic and 100 diastolic. The Wassermann reaction was negative.

Digitalis was given, 1 Gm daily for two days and 0.1 Gm daily thereafter. A week later she reported that the nocturnal dyspnea had disappeared but that the dyspnea on exertion was unchanged. Since that time, two years ago, she has been free from nocturnal dyspnea and has taken digitalis at intervals with questionable effects on her dyspnea on exertion.

CASE 3—L C, an obese Negress, aged 43, complained of dyspnea and palpitation on the slightest exertion. These symptoms had been becoming progressively worse for seven months. She was unable to walk across the room without stopping to rest. For several weeks she had been forced to sit up to breathe at night, and she now was unable to sleep in bed even with three pillows. She would "doze" for a few minutes and then be awakened by dyspnea. During the last few days her ankles had been slightly swollen at night. She dated all of her symptoms from an attack of migratory polyarthritis. The heart was slightly enlarged, the point of maximal impulse being 1 cm outside the midclavicular line. The rate was 104. There was a loud blowing apical systolic murmur, and "tic-tac" quality of sounds. The blood pressure was 172 systolic and 100 diastolic. No râles were heard in the lungs. There was no edema.

She was given digitalis, 1.8 Gm in four days and 0.1 Gm daily thereafter. She stated, a week later, that her nocturnal dyspnea was completely relieved and that she was able to walk at a normal pace without dyspnea. After six weeks, digitalis was stopped. Two months later she complained of dyspnea with very slight exertion. The drug was readministered and she again improved. In the past two years digitalis has been stopped seven times. On each occasion her dyspnea on exertion has become worse within a few weeks and on one instance nocturnal dyspnea reappeared one month after the drug was discontinued. In each instance there has been a rapid improvement in dyspnea following redigitalization.

CASE 4—M G, the patient, a Negress, aged 37, had had increasing dyspnea on exertion for one year and severe paroxysms of dyspnea and cough at night for five weeks. There had never been any edema.

Physical examination revealed an obese woman with severe orthopnea. The point of maximal cardiac impulse was in the sixth interspace, 4 cm outside of the midclavicular line. All the sounds were exaggerated, the heart was overactive, there was a double apical gallop. The aortic second sound was accentuated and the pulmonic second sound more so. There was a loud high-pitched musical systolic murmur. The blood pressure was 160 systolic and 88 diastolic. The lungs were clear. The liver was not felt, there was the slightest pitting edema. The Wassermann reaction was "anticomplementary." The electrocardiogram showed sino-auricular rhythm. Teleoroentgenograms revealed moderate cardiac enlargement and dilatation of the aortic arch.

The patient was given 16 cc of tincture of digitalis immediately, 4 cc the following day and 25 drops daily thereafter. Five days later she reported that she had slept better the first night and had had no nocturnal dyspnea since then, her dyspnea on exertion was much improved.

For the past two years she has received digitalis most of the time. She has had one frank attack of congestive failure with edema, otherwise she has done fairly well.

CASE 5—W. T., the patient, a Negro, aged 52, complained of progressive dyspnea on exertion for two months, and of severe paroxysms of nocturnal dyspnea for five weeks. At first he would only be awakened once each night but more recently the paroxysms had occurred whenever he went to sleep, and he had to sit up all night.

Examination revealed orthopnea, marked cardiac enlargement, a gallop rhythm, a faint apical systolic murmur, general arteriosclerosis and tenderness in the liver region. The blood pressure was 170 systolic and 130 diastolic. There was no edema. He was given digitalis, 1 Gm immediately, 0.5 Gm the following day and 0.2 Gm daily thereafter. Nine days later he said that he had felt a little better for the first two days but that he was now worse than before, he was having severe paroxysmal dyspnea, and his dyspnea on exertion was worse. There was slight pitting edema.

CASE 6—R. O. E., the patient, a white man, aged 55, had had dyspnea on exertion since influenza a year previously. During the past month this had increased, and he had been unable to carry on his usual work as construction superintendent. In the past three weeks he had had four attacks of nocturnal dyspnea, and had also noted substernal pressure brought on by exertion and relieved by rest. The heart was slightly enlarged, the point of maximal impulse being 2 cm outside the midclavicular line. The rate was 80. There were occasional premature beats, there were no murmurs. The arteries were moderately thickened. The blood pressure was 115 systolic and 70 diastolic. Electrocardiograms showed a left ventricular preponderance. He was given digitalis, 1.8 Gm in three days and 0.2 Gm daily thereafter. Four days later he reported that his dyspnea on exertion was "possibly a little better" and that he had had no paroxysms of dyspnea. After taking digitalis for two weeks he said that was much better, he could walk further and faster and continued to be free from nocturnal dyspnea.

CASE 7—A. H., the patient, a Negress, aged 53, had noticed dyspnea for one month on climbing stairs, and for the last week on less exertion. There had been no paroxysmal nocturnal dyspnea, but for the past few weeks she had had to sleep on two pillows. She had never had edema. The pulse rate was 96, about every fifth beat was premature. The point of maximal cardiac impulse was very forceful in the fifth interspace about 14 cm from the midsternal line. The mitral first sound was normal in quality. The pulmonic second sound was slightly

accentuated and the aortic second sound was markedly so, there was a presystolic gallop at the apex and a soft apical systolic murmur. The blood pressure was 186 systolic and 138 diastolic. There were no râles in the lungs, the liver was not felt and there was no edema.

She was given 16 Gm of digitalis in four days and then 0.2 Gm daily. A week later she was seen again and complained of anorexia and nausea but no vomiting. She stated that her dyspnea was very much better. The point of maximal impulse was 12 cm from the midsternal line, the gallop rhythm and extrasystoles had disappeared. The blood pressure was 220 systolic and 140 diastolic. The patient did not return to the clinic again.

CASE 8—J. W. K., the patient, a Negro, aged 34, had been short of breath on walking slowly uphill, for thirteen months, he had been a little worse recently. He had had no dyspnea when walking on the level and no paroxysmal dyspnea or edema.

Physical examination revealed a slightly enlarged heart, as shown both by percussion and roentgenography. The aortic second sound was ringing, a very faint diastolic murmur was heard along the left sternal border. The blood pressure was 170 systolic and 100 diastolic. Repeated Wassermann tests of the blood were negative. The patient was given digitalis, 18 Gm in three days and then 0.2 Gm daily. Two weeks later he reported that the dyspnea was less severe. At the end of another month he was still improved and had dyspnea only when running.

CASE 9—J. R., the patient, a Negro, aged 57, had numerous complaints referable to various systems. For an indefinite period he had had dyspnea on exertion but no paroxysmal dyspnea or edema. The only positive findings were arteriosclerosis, a blood pressure of 180 systolic and 120 diastolic, a pulse rate of 100 and a slight cardiac enlargement. During the two years in which he was followed he was thoroughly digitalized twice. On neither occasion could he report an improvement in his dyspnea.

CASE 10—J. S., the patient, had had increasing dyspnea on slight exertion for a month. He also had had a chronic cough for an indefinite period. He had had no nocturnal dyspnea or edema.

Examination revealed marked cardiac enlargement, a blood pressure of 108 systolic and 80 diastolic, with marked alternation and very loud heart sounds. The electrocardiograms showed notching of the QRS complex, inverted T 1 and T 2 and a left ventricular preponderance. Following digitalization—12 Gm in three days, followed by 0.2 Gm daily—he reported that his shortness of breath was very much better. Three months later digitalis was stopped and within a month he again noted dyspnea on slight exertion. He was redigitalized, and ten days later said that he could perform ordinary activities with comfort and was dyspneic only with severe exertion.

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MECHANISMS OF THE CONTRACTION AND EVACUATION OF THE GALLBLADDER

LATHAN A CRANDALL, JR, M D, P H D

CHICAGO

The factors concerned in the contraction and evacuation of the gallbladder have been greatly clarified by Ivy and his collaborators,¹ who have shown that the introduction of acid or of digested fat into the duodenum liberates a hormone, named by them "cholecystokinin," which causes an active contraction of the viscus. Their work indicates that this liberation of cholecystokinin is one of the principal mechanisms by which evacuation of the gallbladder is effected. In view of their reports, an evaluation of other possible mechanisms is of importance.

REFLEX AND DIRECT STIMULATION OF THE EXTRINSIC NERVES

The literature on the extrinsic nerves of the gallbladder was reviewed in 1924 by Mann,² who was led to conclude that the vagus is mainly motor and the splanchnic mainly inhibitory. Experimental work up to this time had been largely concerned with stimulation of the nerves under anesthesia and by means of drugs, but several investigators have subsequently used more physiologic methods. Whitaker³ filled the gallbladders of dogs with iodized oil and placed shielded electrodes on the vagus, stimulation of the vagus some time after recovery from the anesthesia did not result in any change in the shadow of the gallbladder. He also found that the gallbladder reacted normally to a meal after section of both the vagus and the splanchnic. To study the effects of stimulation of the splanchnic in human beings he injected epinephrine, but observed no response. Copher and Kodama⁴ visualized the gallbladders of dogs by injection of dye and were unable to find any definite evidence of control by the vagus or

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From the Department of Physiology and Pharmacology, Northwestern University Medical School

1 Ivy, A C, and Oldberg, E. *Am J Physiol* **86** 599, 1928. Lueth H C, Ivy, A C, and Kloster, G. *Am J Physiol* **91** 329, 1929. Ivy, A C. *Proc Internat Assemb Inter-State Post-Grad M A, North America* (1929) **5** 378, 1930.

2 Mann, F C. *Physiol Rev* **4** 251, 1924.

3 Whitaker, L R. *Am J Physiol* **78** 411, 1926.

4 Copher and Kodama. Unpublished quoted by Graham et al (footnote 14)

splanchnic Boyden⁵ found that epinephrine injected intravenously into cats produced a diminution of the size of the shadow of the gallbladder Burget,⁶ however, expressed the belief that this is due to relaxation of the distal end of the common bile duct rather than to contraction of the gallbladder Birch and Boyden⁷ found changes in the shape of the gallbladder occurring reflexly on electrical stimulation of the stomach and large intestine in unanesthetized animals Sosman, Whitaker and Edson⁸ observed no effect on the human gallbladder from the sight, smell, or taste of food, nor did they find any consistent effect as a result of subcutaneous injections of atropine, physostigmine, pilocarpine or epinephrine in human beings Whitaker⁹ stated that letting a hungry dog take food into its mouth is without effect on the shadow of the gallbladder Boyden and Birch¹⁰ found that "smelling of food has no effect upon the gallbladder," although later Boyden¹¹ reported that when patients are allowed to smell bacon there is a momentary discharge of bile According to Elman and McMaster,¹² who worked on dogs, the taking of food is immediately followed in most cases by a brief increase in pressure in the gallbladder and a decrease in the resistance offered by the common bile duct to the outflow of bile

EFFECTS OF SHAM FEEDING ON EVACUATION OF THE GALLBLADDER

In view of the contradictory reports in the literature on the action of the extrinsic nerves, it was felt that further experimental work was indicated Sham feeding suggested itself as a method of attack on this problem, since it is well known that sham feeding reflexly stimulates the vagus, markedly increasing the secretion of gastric juice and to a slight extent the secretion of pancreatic juice, as well as influencing the motility of the gastro-intestinal tract A review of the literature failed to show any report on the use of sham feeding in this connection Accordingly, four dogs were prepared with esophageal and gastric fistulas The gallbladders of these animals were visualized, and they were allowed to drink egg yolk or to eat chopped meat for

5 Boyden, E A Anat Rec **33** 201, 1926

6 Burget, G E Am J Physiol **81** 422, 1927

7 Birch, C L, and Boyden, E A Am J Physiol **92** 301, 1930

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9 Whitaker, L R The Mechanism of the Gallbladder and Its Relation to Cholelithiasis, J A M A **88** 1542 (May 14) 1927 Krause, W F, and Whitaker, L R Am J Physiol **87** 172, 1928

10 Boyden, E A, and Birch, C L Proc Soc Exper Biol & Med **24** 827, 1927

11 Boyden, E A Proc Soc Exper Biol & Med **25** 99, 1927

12 Elman, R, and McMaster P D J Exper Med **44** 151, 1926

from one-half to one hour. In three of the animals the gastric juice was withdrawn from the stomach every five minutes during the period of sham feeding, in the fourth dog it was not removed, nor did leakage occur through the gastric fistula. Six tests were made on these four animals, and in no instance did sham feeding cause any apparent change in the size or density of the shadow of the gallbladder. In each case the gallbladder evacuated completely after the introduction of egg yolk into the stomach through the gastric fistula. The dogs were all in good condition and hungry at the time of the experiments.

EFFECTS OF PSYCHIC STIMULI ON EVACUATION OF THE GALLBLADDER IN HUMAN BEINGS

To test the effects of psychic stimuli on the evacuation of the gallbladder in human beings, two healthy male medical students were given intravenous injections of dye and fasted for more than forty-eight hours. During this time they were repeatedly subjected to the sight and smell of food which others were eating¹³. In neither case was there evidence of emptying of the gallbladder as a result of the psychic stimuli.

EFFECTS OF DIRECT STIMULATION OF THE VAGUS AND SPLANCHNIC NERVE ON EVACUATION OF THE GALLBLADDER

In view of the negative results of sham feeding and of psychic stimuli, it was decided to repeat the experiments of previous workers in the direct stimulation of the vagus and splanchnic nerve. In three dogs shielded electrodes were placed on the peripheral end of the right vagus, just above the diaphragm, the left vagus was similarly treated in one dog. Ether anesthesia and aseptic technic were used. At the same time the gallbladders of these animals were filled with iodized or brominized oil. Stimulation of the peripheral vagus with a tetanizing current on the following day for from one-half to one hour caused audible borborygmi but did not result in any expulsion of oil into the duodenum. Similar stimulation of the right splanchnic nerve in one dog whose gallbladder was filled with iodized oil was likewise without effect. All the animals responded to a fat meal or to the intravenous injection of cholecystokinin by the expulsion of considerable amounts of the radiopaque oil from the gallbladder. Stimulation of the

¹³ The results of these experiments on human beings, as well as all the other human experiments, are reported by the courtesy of Dr. James T. Case, Professor of Roentgenology, Northwestern University Medical School, under whose auspices they were performed, and of Dr. E. R. Crowder, Fellow in Roentgenology, who assisted in the human experiments.

splanchnic in one human subject was attempted by the subcutaneous injection of 0.5 cc of epinephrine, there was no resulting change in the shadow of the gallbladder, although emptying occurred following a fat meal. In a personal communication, Dr. Case¹³ stated that he had had consistently negative results in fifteen such experiments, although he had injected as much as 1 cc of epinephrine.

Thus all attempts to induce contraction of the gallbladder by means of artificial direct stimulation or normal reflex stimulation of the vagus and splanchnic in human beings and dogs were unsuccessful, which agrees with the results obtained by the majority of previous workers. Sham feeding is the strongest normal type of reflex excitation of the digestive processes that are under the influence of the vagus. Since sham feeding in the dog and psychic stimuli in man do not affect the shadow of the gallbladder, it is probably not necessary for the patient who has been given the Graham test to avoid the sight or smell of food.

SPONTANEOUS EMPTYING

Graham and his associates¹⁴ brought forth evidence pointing to spontaneous emptying, which they ascribed to a washing out of the bile in the gallbladder by freshly secreted bile from the liver. Whitaker⁹ stated that he had observed in dogs spontaneous emptying of gallbladders filled with "light iodized oil," but offered no explanation for the phenomenon. Iodized poppy-seed oil 40 per cent, which had been used by many workers for filling the gallbladders of experimental animals, has a viscosity of 90 at 20 C (water taken equal to 1), while the average viscosity of eight samples of the bile from dogs' gallbladders was found to be 1.8 at 38 C (maximum 2.2, minimum 1.4). A much greater force would be necessary to empty the highly viscous iodized poppy-seed oil than to expel the bile in the gallbladder. Accordingly the gallbladders of seven dogs were filled with a radiopaque brominized oil having a viscosity of 5.3 at 38 C, since the viscosity of this oil approaches so much more closely that of the bile of the gallbladder, normal conditions were more nearly approximated. In all seven dogs the gallbladders emptied spontaneously, in most cases they were more than half empty at the end of from eighteen to twenty-four hours. It was considered that the nonoccurrence of spontaneous emptying in gallbladders filled with iodized poppy-seed oil might have been due to the fact that the oil was too viscous to pass the sphincter of Oddi. Four dogs were prepared with cannulas in the intramural portion of

14 Graham, E. A., Cole, W. H., Copher, G. H., and Moore, S. Diseases of the Gall Bladder and Bile Ducts. Philadelphia: Lea & Febiger, 1928.

the common bile duct and extending into the lumen of the duodenum, so that resistance in the intramural portion of the duct and in the sphincter would be eliminated. When the gallbladders of these animals were filled with iodized poppy-seed oil, spontaneous emptying took place comparable to that observed when the gallbladder was filled with a light brominized oil.

Spontaneous emptying of the human gallbladder after visualization by tetiothalein sodium has apparently not been observed. According to Sosman, Whitaker and Edson⁸ and Krause and Whitaker,⁹ even a meal

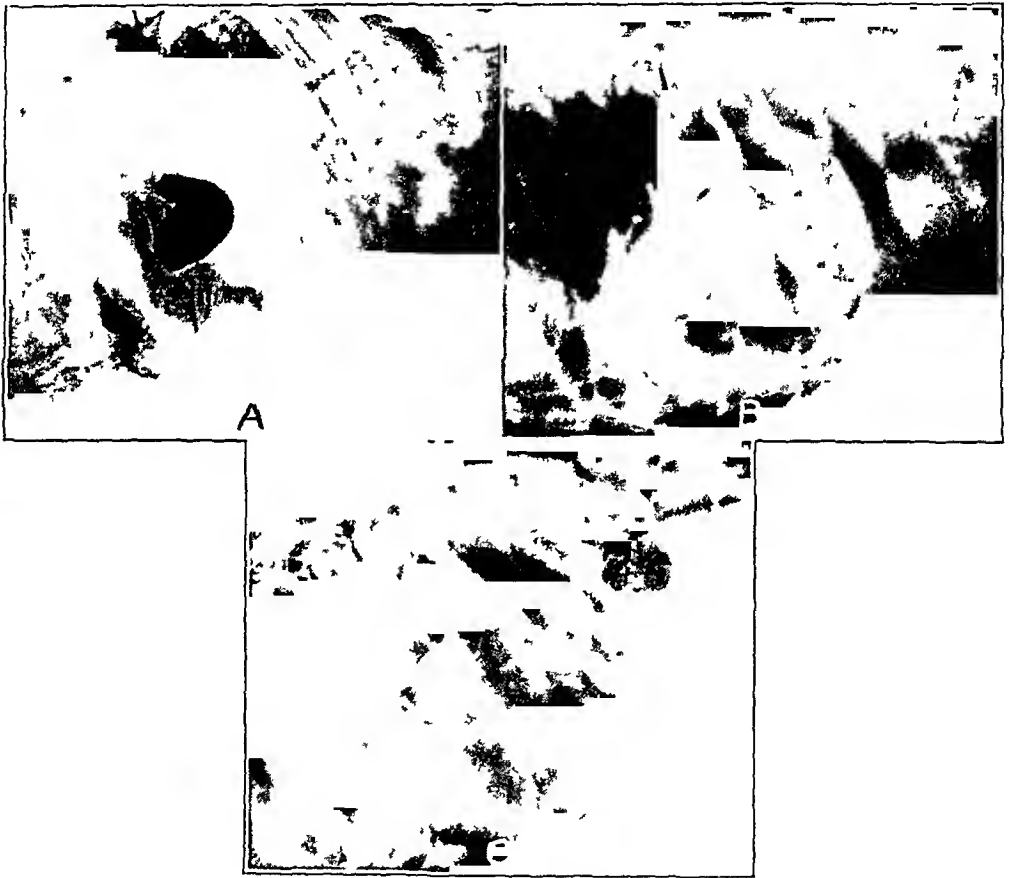


Fig 1—Gallbladder filled with brominized oil with viscosity of 53, showing spontaneous emptying. *A*, fifteen minutes after filling, *B*, six hours after filling, *C*, twenty hours after filling.

of carbohydrates has no effect on the shadow. Case¹⁵ stated that a carbohydrate meal taken one or two hours after intravenous injection of the dye does not interfere with visualization. Four experiments were conducted which confirmed the foregoing reports. Spontaneous emptying in human beings was studied in two subjects, who had received the dye intravenously. Roentgenograms were made through-

¹⁵ Case, J. T. Evaluation of Cholecystography, *J. A. M. A.* **92**: 291 (Jan 26) 1929.

out a period of fasting of fifty and fifty-two hours, respectively. In one of the subjects there was a slight decrease in the opacity of the gallbladder forty-eight hours after injection of the dye, in the other there was no evidence of emptying. In two cases in which carbohydrates alone were eaten following visualization of the gallbladder in human beings, the shadow definitely though slowly decreased in density, the change being distinctly appreciable within twenty-four hours. Lueth¹⁶ showed that each peristaltic wave of the duodenum in anesthetized dogs is associated with a decrease in the resistance to the flow of bile into the intestine. Others ascribed the emptying of the gallbladder entirely to intestinal motility. The slow emptying of the human gallbladder when fat and protein are eliminated from the diet shows, however, that peristalsis in the duodenum is not the primary factor in the rapid emptying that occurs following a mixed meal. Spontaneous emptying of oil, as observed in the dog, may be a result of contractions that are secondary to the trauma caused by the injection of the oil, although in general any injury to the viscus tends to delay rather than to stimulate emptying. In human subjects the relatively long persistence of the shadow may conceivably be ascribed to a reabsorption and reconcentration of any expelled dye, facilitated by an empty gastro-intestinal tract.

COMMENT

The purpose of this study is not the evaluation of all of the factors that may cause minor changes in the tonus of the gallbladder or effect the expulsion of small amounts of bile, it is rather the determination of what mechanisms are responsible for the relatively complete emptying that indubitably occurs following a mixed meal. This has variously been ascribed to a reflex stimulation involving the extrinsic nerves, to duodenal motility with relaxation of the sphincter of Oddi, to the effects of respiratory movements and to elastic recoil of the distended viscus. More recently Ivy¹ has shown that the specific effect of digested fat is the liberation of a hormone which causes contraction of the musculature of the gallbladder and may produce almost complete emptying. Space does not permit a complete discussion of all of the theories that have been advanced to explain the evacuation of the gallbladder. Most workers are now agreed that it is largely effected by contraction of the smooth muscle in the wall of the viscus. The resistance offered by the intramural portion of the common bile duct undoubtedly plays a part, since it has been shown that the pressure necessary to eject bile through the duct may vary within wide limits,

¹⁶ Lueth, H. C. Unpublished work.

and that bile usually enters the duodenum in spurts synchronous with the waves of peristalsis. That this is not a major factor is shown by the facts that, after section of the common bile duct, emptying occurs relatively slowly (Boyden and Birch¹⁰), that emptying is likewise slow when the diet is limited to carbohydrates, and that physostigmine, which increases peristalsis, and epinephrine, which relaxes the intestines, have no marked effect on the shadow of the gallbladder. Boyden⁵ especially has brought forth evidence that the extrinsic nerves exercise some control over the motility of the gallbladder. His experiments with the intravenous injection of epinephrine may be regarded as unphysiologic, and in the hands of several workers epinephrine injected subcutaneously had been ineffective (Whitaker,³ Sosman et al.,⁸ Case¹³). He found that reflexes set up by electrical stimulation of the stomach or of the large intestine may cause changes in the shape of the gallbladder and the evacuation of small amounts of bile, but that such reflexes do not cause massive emptying similar to that provoked by a meal containing fat or protein. The extrinsic nerves seem to play only a minor rôle, if any, in the normal functioning of the organ. The washing out of the contents of the gallbladder with fresh bile from the liver, as suggested by Graham, in conjunction with the part played by duodenal motility, may result in the gradual evacuation of the contents of the gallbladder over a period of many hours, in the absence of a specific stimulus. It is possible that the liberation of cholecystokinin by the action of fat in the stomach may assist somewhat in evacuation (Drewyer and Ivy¹⁷). The present study, however, indicates that the liberation of cholecystokinin from the upper intestine by the action of fat or of acid is chiefly responsible for the rapid and complete emptying of the gallbladder in response to a mixed meal, duodenal motility facilitating the process.

CONCLUSIONS

1 Sham feeding and direct stimulation of the vagus and splanchnic nerve in dogs, and psychic stimuli and the injection of epinephrine in human beings have not been found to have any effect on the motility of the gallbladder.

2 The gallbladders of dogs when filled with brominized oil that is less than three times as viscous as bile empty about one half of the oil spontaneously in from eighteen to twenty-four hours.

3 The gallbladders of dogs when filled with iodized oil of the usual relatively high viscosity empty about one-half spontaneously in from

¹⁷ Drewyer, G. E., and Ivy, A. C. *Proc. Soc. Exper. Biol. & Med.* **27** 186, 1929.

twelve to twenty-four hours when the resistance of the intramural portion of the common bile duct is eliminated

4 In fasting human subjects little tendency toward spontaneous emptying of the gallbladder is observed

5 In human subjects on a carbohydrate diet there is a tendency toward emptying of the gallbladder over a period of from twenty-four to forty-eight hours

6 It is concluded that the liberation of cholecystokinin by the action of fat or of acid in the intestine is the major factor concerned in the contraction and evacuation of the gallbladder that follow a mixed meal. Duodenal motility facilitates this process

PROPHYLAXIS OF POSTOPERATIVE PNEUMONIA BY ORAL HYGIENE

A PRELIMINARY REPORT [†]

SIGMUND W A FRANKEN, D D S
NEW YORK

For the past two decades, serious consideration has been given to the etiology and prevention of postoperative pneumonia. In a large majority of the well organized hospitals, suggestions made by such men as Whipple,¹ Elwyn² and Henderson³ are now incorporated as a matter of routine. These suggestions include

- 1 The better protection of the patient from chills and drafts before, during and after operation and in his journey to and from the operating room
- 2 The use for abdominal operation of bandages of a type that will aid in relieving the pain of breathing and permit deeper inhalation
- 3 The use of opiates for a few days post operation to facilitate breathing by elimination of pain
- 4 The inhalation of carbon dioxide and oxygen at the termination of general anesthesia, for ventilating and removing the anesthetic from the lungs to restore normal breathing
- 5 The postponement of operations in the presence of active or recent disturbances of the upper respiratory tract
- 6 The choice of anesthesia and its administration by a trained personnel

Among other factors in the causation of postoperative pneumonia are

- 1 The site of operation
- 2 The presence of latent pulmonary disease
- 3 The aspiration of septic material from the mouth

Among these causes and factors, the aspiration of septic material from the mouth during anesthesia probably contributes the largest share of potential danger to the patient, indeed, Featherstone⁴ quoted Prof

[†] Submitted for publication, March 28, 1931

[†] From the Dental Service, Lenox Hill Hospital

[†] Read before the New York Academy of Medicine, Section of Surgery and Rhinology, Dec 6, 1930

1 Whipple, A O Post-Operative Pneumonitis, Surg, Gynec & Obst **26** 29 (Jan) 1918

2 Elwyn, Herman Post-Operative Pneumonia, J A M A **79** 2154 (Dec 23) 1922, **82** 384 (Feb 2) 1924

3 Henderson, Yandell Acapnia as a Factor in Post-Operative Shock, Atelectasis and Pneumonia, J A M A **95** 572 (Aug 23) 1930

4 Featherstone, Henry An Inquiry into the Causation of Post-Operative Pneumonia, Brit J Surg **12** 487 (Jan) 1925

J Shaw Dunn of the chair of pathology at Birmingham (England) in saying that aspiration pneumonia is the commonest form of postoperative pneumonia. Obviously, it is not possible to prevent entirely the aspiration, but it seems that a reduction of its septic and filthy properties might be feasible and of extreme value. Not only because little, if any, work had been done along these lines, but because this particular field of prophylaxis lay within the province of the dentist, I was moved several years ago to suggest to the attending surgeons of the Lenox Hill Hospital that we strive to eliminate the infectious condition of the mouth before operation, and thus test the validity of this hypothesis. Although the proposal met with immediate cooperation and aid, our procedure at the outset was, of necessity, makeshift, for the dental department was not sufficiently manned for the undertaking. However, as an initial step in the preoperative oral care of surgical patients, we made a brief trial in 1925, selecting the medical pneumonia season of February and March. We subjected the patients in one of the active surgical services to the new routine and used those in the other service as controls.

I regret to say that the result of six weeks' trial was discouraging, for a patient in the service receiving oral care developed postoperative pneumonia on the last day of the experimental period. But the fact that the patient had had a hernioplasty performed under a local anesthetic did much to mitigate a natural disappointment, and we decided to continue the experiment at a later date, for the intensive preoperative oral care of the surgical patients, in addition to the care of all the other ward patients, for more than a limited period, proved too severe a physical strain on the dental intern. Therefore, continuing with the February and March seasons of the following and succeeding years, we alternated each year from one surgical service to another, and gave the patients during that time complete preoperative oral care. Then, early in 1928, on the appointment of a dental prophylactic nurse to the staff to assist the intern, we began at the end of February of that year with a full and complete dental routine for the preliminary care of all the operative patients in the surgical and genito-urinary services. No other changes were inaugurated in the treatment or handling of surgical patients. The usual care was continued, with only the addition of the intensive oral care by the dental department.

TECHNIC

Adhering to the general fact that patients with nonemergency cases are admitted to the hospital for observation from two to four days prior to operation, the dental department contrives to do its work during that period. This can, and is, done without interfering with the patients' usual preoperative surgical routine of examinations, laboratory tests and observation.

As soon as possible after admission to the wards, the patient is sent to the dental room, which is situated near the surgical wards. First, the gums and teeth are thoroughly swabbed by the dental hygienist with a solution consisting of

Zinc chloride	15 parts
Aqua destillata	10 parts
Iodine crystals	25 parts
Glycerin	50 parts

After the swabbing, the teeth are thoroughly scaled and polished, and the condition of the mouth is charted, on a separate dental sheet of a distinguishing color, as to carious teeth, teeth to be extracted, missing teeth, condition of the soft parts and the presence of crowns and bridges. The patient is also instructed in the proper use of a toothbrush, and, if without, he is presented with a good, serviceable one. This toothbrush is not the usual clinic type, with bamboo handle, but has a good bone handle with seven pairs of double-row bristles.

The patient then returns to the ward, where the medical nurse sees that he uses hourly a mouth wash consisting of a 2 per cent formaldehyde solution—a teaspoonful to one-half glass of water. In the event of infected roots or teeth, the dental intern immediately begins to extract one at a time, at intervals of twenty-four hours, and then only if there has been no unfavorable reaction after the first or subsequent extractions. If any reaction, such as a rise of temperature, should occur post extraction, the intern is not permitted to continue until not only the subsidence of symptoms takes place, but also a consultation is held with the surgical staff as to the advisability of further extractions. Extractions are never done in the twenty-four hours immediately preceding the scheduled surgical operation.

On the second morning after admission, the patient's mouth is again swabbed with the solution used immediately after admission, and the formaldehyde mouth wash is used every hour. This daily swabbing and hourly mouth wash are continued up to the time the patient leaves the ward to go to the anesthesia room, where he gets the final swab and mouth wash.

This completes the technic incorporated for periods of about six weeks up to Feb 26, 1928, when, with the appointment of a dental hygienist, we continued to give the preoperative oral care described through the entire year. Although the work is still being carried on, our report ends on Feb 26, 1930, completing two years of intensive work. Unfortunately, this does not give us as large a number of patients as we should wish, as the figures are depleted by the large percentage of patients who did not go to operation as well as by the number of those who were transferred to other services. Emergency operations are also excluded from the report, but we hope to work out a rapid technic that may be used in such instances. The results on the 859 patients, however, show such a marked decrease in the cases of pneumonia that I feel justified in offering the report as it stands, and trust that in time we shall be able to base our findings on the same number of patients as do Whipple, Cleveland, Elwyn and others.

It is of value to study the figures given by Featherstone on the number of cases of postoperative pneumonia reported from various sources. Those cited prior to 1919 have been omitted from this report but the

figures of the Lenox Hill Hospital have been added (table 1) The table given by Featherstone shows a low of 2.6 per cent and a high of 8.5 per cent, whereas the patients who have had preoperative oral care at the Lenox Hill Hospital show an incidence of 0.81 per cent of postoperative pneumonia

It is also interesting to note (table 2) that in 1927, at the Lenox Hill Hospital, of 975 noncontrolled patients operated on, 25 developed post-

TABLE 1—*Figures Given by Featherstone on the Number of Postoperative Pneumonias Reported from Various Sources, with Those of Lenox Hill Hospital Added*

Year	Patients Operated on	Pneumonias	Incidence, per Cent
1919 Cleveland	1,940	65	3.30
1918 Whipple	3,719	97	2.60
1921 Mandl	1,585		8.50
1922 Herb	1,534	76	5.00
1922 Elwyn	2,932	81	2.76
1924 Elwyn (General)	1,734	52	3.00
1924 Elwyn (Local)	399	11	2.70
Lenox Hill Hospital	859	7	0.81

TABLE 2—*Lenox Hill Hospital Figures Incidence of Postoperative Pneumonia Before and After Establishment of Preoperative Oral Care*

Year	Patients Operated on			Incidence per Cent
	Without Preoperative Oral Care	With Preoperative Oral Care	Post operative Pneumonias	
1927	975		25	2.5
1928		298	2	0.7—
1929		419	3	0.7

TABLE 3—*Figures Given by New York City Board of Health Showing Rise in Number of Cases of Pneumonia Throughout the City*

Year	Cases of Pneumonia	Case Rate per 100,000 Population
1927	18,273	306
1928	21,079	350
1929	21,132	358*

* An increase of approximately 16 per cent

operative pneumonia—an incidence of 2.5 per cent, which compares favorably with the current low reports to that date, also that, although no other measures were employed, the results during 1928 and 1929, up to Feb. 26, 1930, when the routine of oral care was strictly carried out, show an incidence of 0.7 per cent

The question arises whether there was a decided drop throughout the city in medical pneumonias during those particular two years. An inquiry at the New York City Board of Health elicited the reply shown in table 3. This indicates a rise from 306 per hundred thousand of

population in 1927, to 358 per hundred thousand, in the greater city. This is a rise of approximately 16 per cent throughout Greater New York. During this same period, the patients at the Lenox Hill Hospital who received preoperative oral care showed a decrease in the incidence of postoperative pneumonia: only 5 of 717 patients who received preoperative oral care developed postoperative pneumonia, as compared with 25 of 975 patients who did not receive such care. This represents a reduction of from 2.5 per cent to 0.7 per cent, or a little more than two thirds.

Table 4 indicates the regions of the body operated on, the numbers of operations performed and the numbers of postoperative pneumonias with the incidence per cent. Of the 468 abdominal operations, 4 led

TABLE 4—*Regions of Body Operated on, Numbers of Postoperative Pneumonias and Incidence per Cent*

Region Operated on	Operations	Postoperative Pneumonias	Incidence per Cent
Abdomen	468	4	0.86
Rectum	146		
Genito-urinary organs	42	2	4.80
Head and neck	51	1	2.0
Thorax	35		
Extremities	117		
Total	859	7	0.81

TABLE 5—*Types of Anesthetics, Number of Postoperative Pneumonias and Incidence per Cent*

Anesthetics	Postoperative Pneumonias	Incidence, per Cent
General, 668	3	0.5
Local, 149	3	2.0
Colonic, 6	1	16.6
Spinal, 36		
Total, 859	7	0.81

to postoperative pneumonia, or 0.86 per cent. Three of these were operations for hernias, and the fourth was performed on a young boy who underwent two laparotomies within a short time, the pneumonia developed after the second operation. The two in the genito-urinary service were prostatectomies performed on old men. The one patient in the head and neck division was under colonic anesthesia for a long period—over five hours. He underwent the removal of a carcinoma of the cheek, the cervical glands were dissected, and a plastic operation was performed.

Table 5 indicates the various types of anesthetics employed. The figures for patients operated on under general anesthesia are most gratifying, with an incidence per cent of only 0.5. Of the three patients operated on under local anesthesia, with an incidence per cent of 2, it

was disclosed, on examination of the case histories, that two had had hernioplasties and the third a prostatectomy. The high percentage for those operated on under colonic anesthesia is due, possibly, to the fact that we have so few to report on. The patient who developed the post-operative pneumonia was the one mentioned as having had the long experience in the operating room.

All of these records of patients suffering from postoperative pneumonia were taken from the history charts, and the diagnoses were always made by the surgical and medical staffs. After the routine preoperative oral care was completed, the dental department had no further contact with the patients. Reports were received from the record room.

SUMMARY

For the successful execution of a work of this nature, it is essential for the dental department to have the full cooperation of both the surgical staff and the superintendent of nurses. At the Lenox Hill Hospital, I received encouragement and aid from these sources.

By the use of this technic, which has been developed over the past five or six years, we believe that the mouth can be put into a reasonably clean, hygienic state before the operation is performed. At various times, suggestions for milder methods have been presented by those cognizant of the work, but at each substitution the results proved to be less beneficial to the patient, and we have always reverted to the routine described.

This preliminary report on 859 surgical patients who were given definite preoperative oral care indicates a measurable drop in postoperative pneumonias. In the figures submitted, this drop amounts to two-thirds, and as nothing was changed and no other measures were taken, it seems to point out the practical value of a standard preoperative oral routine. This routine can be established in any general hospital with comparatively small expenditure, but it requires constant cooperation and surveillance.

26 East Thirty-Sixth Street

AZOTEMIA WITH NORMAL KIDNEYS FOUND POST MORTEM

POSSIBLE CAUSE LOW BLOOD PRESSURE AFTER OPERATION ²

THEODORE S EVANS, M D
NEW HAVEN, CONN

The physiologic processes of the kidney require certain constant factors. The tissue of the kidney must be normal if it is to concentrate the sodium chloride of the blood and maintain it at a constant level and if it is to maintain the nitrogenous factors of the blood at a normal level. The blood pressure must be within certain normal limits if the kidney is to secrete properly fluid and other products in solution. If the blood pressure is to be maintained at a certain level, the heart or propulsive force must be adequate, and the blood vessels must have a certain tone and consistency. The failure of any of these functions individually results in the failure of the general excretory functions of the kidney as a whole.

Physicians are familiar with the pictures that result from damage to the arteries and other blood vessels of the kidneys and those that result from damage to the secretory cells of the kidney. Ambard, Volhard and Fahl, Floyd and others have demonstrated the relation of this type of damage to hypertension, cardiac hypertrophy and damage of the tissues, and azotemia. The converse relation of hypertension or so-called malignant hypertension without much demonstrable arterial damage to failure of the function of the kidney and heart failure is also well known. During recent years it has been demonstrated by Atchley and his school that a condition similar to the well known "surgical shock," with a sudden fall in the blood pressure and death, occurs frequently. These workers pointed out the fact that such cases of vascular failure were frequently erroneously called "heart failure" and that even in the presence of signs of edema of the lungs, the treatment accorded in cases of surgical shock—the intravenous administration of physiologic solution of sodium chloride, dextrose and blood—was effective in saving life. However, the cases described by Atchley showed evidences of circulatory failure in the lungs and elsewhere and did not show any considerable rise in the nitrogenous components of the blood. Lastly, Floyd has described cases of mechanical failure of the kidneys due to sudden, almost complete destruction of the kidney by embolic abscesses or infarcts.

² Submitted for publication, March 2, 1931

The case report in this article is demonstrative of a condition a description of which I have not been able to find in the literature. The case was one of acute renal failure with anuria and resulting fatal azotemia, clinically similar to that seen in scarlet fever and poisoning with corrosive mercuric chloride, but differing greatly from it in certain respects. The anuria was followed much more promptly by death than in cases due to scarlet fever or poisoning with mercury. The nitrogenous factors in the blood rose much faster than in the other conditions. The blood pressure in this case was uniformly very low. At autopsy, the renal, hepatic and cardiac tissues were found to be normal, whereas damage to one or all of these tissues is seen at autopsies performed in cases of scarlet fever or poisoning with mercury.

REPORT OF CASE

History—R. H., a white man, aged 35 years, married, a sales executive, was seen by Dr. Leonard Bacon early in the afternoon of Oct. 21, 1930. He had driven to New Haven from Boston on October 20, and had eaten a large and rather rich evening meal. He had gone to bed on this evening feeling well, but was awakened from sleep at 4 a. m., October 21, by a severe abdominal pain. By the time that Dr. Bacon arrived, at 1:30 p. m., October 21, he had vomited once, with partial relief from pain. There were no other symptoms.

Examination—Physical examination made at this time showed a temperature of 101 F., with a relatively slow pulse rate, about 84. There was abdominal pain and tenderness in the hypogastrium near the midline, but there was no pain or tenderness near McBurney's point. The rest of the physical examination gave normal results. The patient was seen later that afternoon, when it was found that the pain had abated somewhat and that the temperature was higher—104 F.—and the pulse rate, 104. He had not vomited in the interim. At this examination the urine was clear and contained no albumin.

The following morning, the patient was seen again, the temperature had subsided to 101.6 F., and the pulse rate was slow, 84. However, there had been no vomiting. The character and position of the pain had not changed, and the results of physical examination were the same. During the afternoon of this day, more tenderness and pain developed, and there was some localized spasm of the lower portion of the right rectus muscle. The lungs were still clear, the temperature was 104 F., and the pulse rate, 104. A blood count made at this time showed white blood cells, 15,000, polymorphonuclears, 92 per cent. He was sent to Grace Hospital immediately with the diagnosis of acute appendicitis and was admitted there with a temperature of 101.8 F. and a pulse rate of 90. Examination of the urine made at that time showed a high specific gravity and a trace of albumin. There were a few hyaline and granular casts and an occasional red blood cell.

Operation—Operation was performed immediately and, with the patient under ethylene anesthesia, a girdron incision was made over McBurney's point. A mass of inflammatory tissue was felt toward Poupart's ligament. The rest of the peritoneum was found to be in good condition. As the mass could not be delivered easily, the incision was enlarged downward. A gush of seropus followed the insertion of the exploring finger. The omentum was drawn away with the inflamed mass and delivered through the wound. It was indurated and inflamed.

and obviously had acted as an involucre surrounding the gangrenous appendix. The inflamed portion of the omentum was clamped and resected. The appendix was clamped and removed together with the mesentery. There were slight hemorrhage and slight handling of the intestines. About one-fourth inch (6.35 mm) from the cecum the appendix did not show gangrene, and the stump was tied off at this point. The clamped portions were ligated, and the intestines and omentum were dropped back into the abdominal cavity. Three large cigaret drains were inserted, one into the pelvis and two others to the outside of the cecum and ascending colon. Two silkworm gut sutures were passed through the whole abdominal wall and a cigaret drain and gauze pack were inserted along the edges of the wound to act as a plug and to guard against herniation of the intestinal coils through the considerable opening in the abdomen. The patient was taken from the operating table in good condition.

Pathologic Report—The pathologic specimen was a gangrenous appendix which was very thin-walled, collapsed and discolored. There was also some indurated and inflamed fat tissue. Under microscopic scrutiny only a small part of the tissue could be identified as appendix because of the marked gangrene.

Course—The patient did exceedingly well for the first five days after the operation. The temperature immediately fell to normal and remained so through the course. The pulse was consistently slow and for five days was of good quality. The respiratory rate was consistently 22 throughout the course. The patient took fluids exceedingly well and passed copious urine. There was some distention of the abdomen but, considering the magnitude of the pathologic process, the distention was moderate. Flatus was passed early, and several partially formed stools were passed also. There was no postoperative vomiting.

The condition of the patient became slightly worse during the afternoon of the fifth day, but was not alarming, and he had a fairly restful night. Beginning at noon of the sixth day he ceased voiding, and from then on for thirty-eight hours a total of only 75 cc of urine was passed. He did not vomit, but the pulse became steadily weaker and he was very restless. Muscular twitchings also developed.

At noon on October 29, the seventh postoperative day, the patient was seen by me in consultation with Dr. Bacon. He then had a history of practical anuria for twenty-four hours, only 50 cc of urine having been passed since the previous day, though he had taken enormous amounts of fluid. He was very irritable, and twitching of the muscles was evident. The breath was ammoniacal and the eyes sunken. The heart was still slow, but the sounds were weak and the pulse so poor that it could be felt only occasionally at the wrist. The lungs were clear, with no signs of edema. The abdomen was only moderately distended. The liver was not palpable, and dulness was normal. The extremities were cold and blue. The blood pressure was only 50 mm systolic.

It was decided to give an infusion and to take blood to be tested for nonprotein nitrogen at the same time. The following diagnosis was made: (1) anuria, (2) renal failure, (3) probable vasomotor failure, since the heart was apparently normal, and (4) probable azotemia. Apparently this was a case of vasomotor failure resulting in a blood pressure so low that the kidney was mechanically unable to secrete urine.

An infusion of 100 Gm of dextrose was given in a 50 per cent solution followed by the administration of 1,500 cc of saline solution. There was 155 mg of nonprotein nitrogen per hundred cubic centimeters of blood. The reaction to this treatment was spectacular. The patient went to sleep during the infusion and

became free from irritation and muscular twitchings. He slept for about two hours afterward. The blood pressure rose to 90, and the pulse had good volume and was slow. He still took fluids well.

At about 3 p m, he began to be restless again and the muscular twitchings recommenced. The blood pressure dropped to 50 systolic and the pulse was weak, though not nearly so weak as before. He had not secreted urine since the first infusion, so I catheterized him, but only about 20 drops was obtained. Another infusion was given and 100 Gm of dextrose was given intravenously in a 50 per cent solution, followed by the administration of 1,500 cc of saline solution. Again the effect was good, and the patient fell asleep during the infusion. The improvement was short-lived, however. Renal diathermy was tried, but proved ineffective also. At this time the nonprotein nitrogen was 170 mg, a rise of 15 mg (in spite of the large infusion) occurring in three and one-half hours.

The patient became more wild, the muscular twitchings were more marked and the pulse soon relapsed to a very weak beat. The heart sounds were distant, and the blood pressure fell again. He still took fluids well.

At 9 p m, the patient was seen by Dr. George Blumer who obtained the same physical findings as were noted at noon and in the afternoon. The blood pressure had fallen to 60 mm. The extremities were cold again and the pulse barely perceptible. It was Dr. Blumer's opinion also that this was a case of sudden renal failure due to vasomotor dysfunction and resulting from inability of the kidney to secrete urine at such a low blood pressure.

It was felt that any procedure would prove to be only palliative, and so he was made comfortable with the administration of scopolamine hydrobromide and morphine.

Until about 10 p m he took fluids well and did not vomit, but from then on he had severe hiccups and vomited. He died at 2 a m on the following morning. The nonprotein nitrogen was 240 mg.

During the last thirty-eight hours of his life he took by mouth more than 4,500 cc of fluid and received by infusion 3,400 cc of fluid. The total of 7,900 cc is large, but during this period he did not secrete more than 70 cc, at the most.

This was a case of anuria with uremia. The blood pressure was low, there was every reason to suppose that the heart, kidneys and liver would be normal, and at autopsy this proved to be the case.

Autopsy—Autopsy was performed by Dr. Charles J. Bartlett, pathologist, at the Grace Hospital, on October 30. The body was that of a well developed and well nourished man. Rigor mortis and postmortem lividity were present. There was purging from the nose. The abdomen was moderately distended. There was no edema of the ankles. There was an open appendectomy wound about 12 cm. in length with gauze packing.

When the peritoneal cavity was opened, the small intestine was found to be distended with gas, moderately congested and the coils slightly adherent by lymph. There was no general peritonitis or fluid in the peritoneal cavity. Examination of the site of operation showed the field walled off, with no collection of liquid. No drain was present, but there was gauze in the operative wound, extending to the lower part of the abdominal wall. It was such a wound as would be expected in appendectomy in a case of gangrenous appendicitis without generalized peritonitis.

No fluid was found in either side of the thoracic cavity. Both lungs were free. They were rather large and overlapped slightly in the median line. The height

of the diaphragm on the right side was at the fourth rib, on the left side, at the fifth interspace. The heart was of normal size, weighing 310 Gm. The myocardium was firm and of good color. The vessels and coronary arteries were normal. Both lungs showed acute congestion and edema, particularly in the lower lobes, apparently a terminal process. There was some emphysema of the upper lobes.

The spleen was of normal size, weighing 120 Gm. It showed a slight enlargement of the malpighian bodies. The pancreas appeared normal. The stomach and the intestines were normal, except for the distention of the intestines by gas and congestion, and the operative condition at the site of the appendix. The liver weighed 1,740 Gm. It was smooth on the surface and somewhat pale as though there might be some acute parenchymatous degeneration. The suprarenal capsules appeared normal. The combined weight of both kidneys was 280 Gm. The capsules of the kidneys were only slightly more adherent than normal, leaving a granular surface in a few small areas when removed. The cortex was of good thickness and somewhat paler than normal, there was probably a slight cloudy swelling. The bladder was contracted and appeared normal. The prostate was not enlarged. The aorta was smooth and elastic. The following anatomic diagnosis was made: recent operation on appendix, intestines congested and distended, no general peritonitis, acute congestion and edema of lungs, slight cloudy swelling of kidneys and liver, cause of death not apparent from the gross anatomic observations.

On microscopic examination, sections of the kidneys showed that the glomeruli were apparently normal, there was no recognizable increase in connective tissue, and only a small amount of acute parenchymatous degeneration. The liver showed only a slight acute parenchymatous degeneration. Examination of the other organs added nothing to the gross description.

COMMENT

In the light of the normal observations at autopsy, this would appear to be a case of true uremia due to purely mechanical factors: the inability of the kidney to secrete urine at such a low blood pressure, and the consequent rise in the nitrogen factors of the blood. Apparently the basic failure was of vasomotor origin, but what lay behind this is a matter of conjecture, as the suprarenal glands were normal. When compared with cases of scarlet fever and mercury poisoning, the time from the onset of anuria to death was exceedingly short, and this might lead one to suppose that the nitrogen had already mounted to a high point before the anuria began. Possibly this process had begun at the time of operation, but if that were the case, one would expect to find evident changes in the renal tissue.

Though this condition might come under the group termed by Atchley "medical shock," the cases described by him showed signs of circulatory failure, such as edema of the lungs and dyspnea, and did not show a marked rise in the figures for nitrogen. My patient did not have such signs at any time until immediately ante mortem.

Certainly, the amount of fluid taken by the patient through the mouth and introduced by vein was sufficient to give volume to the

circulation. Therefore, it would seem that the failure to maintain a normal blood pressure was due to some factor other than the volume of the blood or the heart. The only remaining factor that can be called to account seems to be the tone of the arterial and venous systems. Had there been a complete relaxation of these muscles with a resulting widening of the vascular bed, a sudden and continued fall in blood pressure might have developed. If this was the case, the only means at hand to combat the condition were used unsuccessfully.

To return to the physiology of the kidney, in this case there was a change in the blood pressure. This change was dependent on the tone of the blood vessels, which was so low that normal blood pressure could not be maintained in spite of what was believed to be adequate treatment. Failure of this type may have been due to toxicity from the gangrenous and ruptured appendix or it may have been a more fundamental inadequacy, since the patient had had a low blood pressure one year previously, when he was refused life insurance because of hypotension. There may even have been a congenital inadequacy in the nerve supply of the vascular structure, which was not severe enough to cause trouble under normal conditions but which could not withstand the sudden strain of an operation. At any rate, in this case apparently an azotemic death occurred, owing to mechanical failure of the kidneys resulting from a blood pressure so low that the kidney could not secrete urine, though the kidneys, the heart, the suprarenals and the liver were undamaged.

EFFECT OF INGESTION OF WATER AND OF DEXTROSE SOLUTION ON EMPTYING TIME OF NORMAL STOMACH

HAIG H KASABACH, M D

NEW YORK

Trainers and coaches of athletic teams generally prohibit the ingestion of fluid by players during the hour immediately preceding athletic contests. One of the popular reasons for this prohibition is the belief that fluid taken prior to the game remains in the stomach (the stomach becoming "water-logged") and may cause nausea and vomiting, thereby impairing the player's efficiency. In recent years it has been a common practice to give athletes, such as football players, carbohydrate by mouth to supply readily available energy and to avoid hypoglycemia, which has been shown by Levine and Gordon¹ to occur in marathon runners. The purpose of this study was to determine the emptying time of the stomach in healthy young men after the ingestion of water and of dextrose solution during periods of rest and exercise.

No evidence was found in the literature to support the popular belief that ingested fluid "water-logs" the stomach if taken prior to athletic contests or during exercise. Apparently accurate experiments on exactly this aspect of gastromotility have not been made previously. However, there have been a few investigations of problems closely related to the one under consideration. The earliest observations on the emptying time of the stomach were those of William Beaumont,² the great pioneer physiologist, on his patient, Alexis St. Martin, who suffered from a permanent gastric fistula. Dr. Beaumont believed that moderate exercise favors rapid digestion by increasing the circulation of the system and the temperature of the digestive tract. Fatiguing exercises, in his opinion, retard the process of digestion. He presented two reasons for these conclusions: "the debility following hard labor, of which the stomach partakes, and the depressed temperature of the system, consequent upon perspiration and evaporation from the system." He also stated that fluids of all kinds pass out of the stomach soon after they are received.

¹ Submitted for publication, Feb. 4, 1931.

² From the Department of Roentgenology, University Hospital, Ann Arbor, Mich.

1 Levine, S. A., and Gordon, B. Some Changes in the Chemical Constituents of the Blood Following a Marathon Race, with Special Reference to the Development of Hypoglycemia, *J. A. M. A.* **82** 1778 (May 31) 1924.

2 Beaumont, William. Experiments and Observations on the Gastric Juice and Physiology of Digestion, Lilly, Wait & Wait & Company, Boston, 1834.

Series of experiments were conducted by Nielsen,³ who selected a group of twenty persons (ten men and ten women) without gastrointestinal symptoms. He examined them by fluoroscope after the ingestion of a meal composed of gruel, 300 Gm of rice flour and 100 Gm of barium sulphate. The first series of experiments was made with the subjects resting in bed, the second with the same subjects walking about. He found that the average emptying time of the men's stomachs was thirty-seven minutes longer while resting in bed than while walking, and that of the women's stomachs thirty-four minutes longer while resting than while walking.

Campbell⁴ studied the gastric content and emptying time of the stomach by fractional extraction with a Ryle tube and by complete withdrawal of the gastric contents at the end of two and one-half hours. In most of his experiments the subjects were seven healthy young men, and the ingesta consisted of a "porridge test meal." He found that exercise (running slowly for 2 or 3 miles) retarded the secretion of gastric juice and decreased the rate of emptying.

For our experiment fifty healthy college students were selected, none of whom remembered having had symptoms of indigestion. All of them were available for the first, or rest, phase of the experiment, and twenty were available for the second, or exercise, phase. They were instructed to abstain from food and drink of any kind after 7 p. m. and to appear at the roentgen department of the University Health Service at 9 a. m. the following morning. Each was given about 500 cc of water containing 1 tablespoonful of skiabaryt, which is 75 to 85 per cent barium sulphate U. S. P., admixed with sugar, tragacanth, cinnamon, vanillin and cacao. This mixture contains just enough opaque material to outline the stomach satisfactorily. Each subject was observed with the upright fluoroscope at fifteen minute intervals until the stomach was empty, and then a flat film of the abdomen was taken. Between observations they were allowed to sit down or stroll around the building as they pleased. The second, or exercise, phase of the problem was carried out with exactly the same technic except that between periods of observation the subjects ran continuously. They ran around the campus or the gymnasium track until it was time to appear for another observation. This procedure was continued until fluoroscopic examination showed the stomach to be empty.

The accompanying table records the results of the observations with both water and dextrose during the periods of rest and exercise. After the ingestion of water, while the subjects were at rest the average

3 Nielsen, A. Roentgenological Examination of the Motility of the Stomach in Healthy Individuals During Rest and Motion, *Acta radiol.* **1** 379, 1921-1922.

4 Campbell, J. M. H., Mitchell, G. O., and Powell, A. T. W. The Influence of Exercise on Digestion, *Guy's Hosp. Rep.* **78** 279, 1928.

emptying time of the stomach was sixty and three-tenths minutes. In thirty-seven of the men, or 74 per cent of the group of fifty subjects, the stomach emptied during the first hour. Of the group of twenty who ingested water and then exercised, fifteen, or 75 per cent, showed total gastric evacuation in forty-five minutes. The average emptying time for the group of twenty was thirty-nine minutes. After the ingestion of a 50 per cent dextrose solution, the average emptying time of twenty subjects at rest was sixty-four and one-half minutes. Fourteen, or 70 per cent of the subjects, showed complete gastric emptying during the first hour. The average emptying time of the same group on taking dextrose solution and exercising was forty-two minutes. Fifteen, or 75 per cent, showed complete gastric emptying after the first forty-five minutes.

It is evident that the difference in the emptying time of the stomach after the ingestion of water and of dextrose solution is negligible. On the other hand, relatively strenuous exercise appears to shorten definitely

Emptying Time of the Stomach in Four Experiments

Emptying Time	500 Cc Water + 1 Tablespoon of Skiabaryt				500 Cc 50% Dextrose Solution + 1 Tablespoon of Skiabaryt			
	Rest		Exercise		Rest		Exercise	
	No of Cases	Per Cent	No of Cases	Per Cent	No of Cases	Per Cent	No of Cases	Per Cent
In 30 minutes	5	10	9	45	1	5	8	40
In 45 minutes	14	28	6	30	6	30	7	35
In 60 minutes	18	36	5	25	7	35	4	20
In 75 minutes	7	14	0	0	2	10	1	5
In 90 minutes	3	6	0	0	2	10	0	0
In 120 minutes	3	6	0	0	2	10	0	0
Total cases studied	50	100	20	100	20	100	20	100
Average emptying time	60.3 minutes		39 minutes		64.5 minutes		42 minutes	

the emptying time after the ingestion of either water or dextrose solution. It is possible that the difference in results between the groups without exercise and those with exercise might have been greater had the former been completely at rest in a reclining position during the period of observation. In these observations no relation between the emptying time of the stomach and the type of habitus of the subject could be determined. The so-called gastropototic or long stomach was as common in young men with good abdominal muscles as in those who were thin and had less developed muscles. It is noteworthy that rest and exercise seem to have little effect on the individual variations in the emptying time found in this group. Stomachs that required a longer time than the average to empty during rest also regularly required longer than the average time to empty during exercise. Similarly, rapid gastric evacuation was seen in the same person during both rest and exercise.

The experiments of Campbell are of particular interest. Running, even at a moderate pace, would ordinarily be considered fairly vigorous exertion. This form of exercise, which apparently retarded the emptying of the stomach in his subjects, seemed to accelerate it in our subjects. This apparent discrepancy may be due, in part at least, to the difference in ingesta. Oatmeal porridge requires a certain amount of gastric digestion, while water and dextrose solution are simply fluids to be expelled, a process that, as Beaumont suggested, occurs relatively quickly. Furthermore, Campbell pointed out in his experiment that the retardation in the time of digestion and emptying of the stomach seemed proportional to the amount of distress caused by the exercise. The young men used in our experiment were vigorous and of athletic habits, and the running in which they indulged during the observations did not distress them.

CONCLUSION

1 The emptying time of the stomach was determined fluoroscopically in fifty healthy young college students after the ingestion of 500 cc of water and of an equal quantity of 50 per cent dextrose solution containing a very small quantity of barium sulphate, with the subjects sitting or walking about, and in twenty cases with the subjects running continuously between observations. The total number of experiments on the fifty students was one hundred and ten.

2 No difference was observed in the rate of emptying of dextrose solution and of water in either group.

3 Exercise (running) seemed to produce a definite acceleration in the emptying time of the stomach. In these experiments, as exercise accelerated the emptying of the stomach, it seems justifiable to conclude that dextrose solution in a palatable form could be administered to athletes before a contest in which readily available fuel is required, without fear of producing gastric retention.

Dr F Lynam, the physician of the Athletic Association of the University of Michigan, and Miss Mary Zeile assisted me in carrying out these studies.

Book Reviews

DIFFERENTIAL DIAGNOSIS IN PEDIATRICS By DR W PFLUGER, with a foreword by PROF DR J HUSLER Price, 73 marks Pp 160 Dresden Theodore Steinkopff, 1931

This modest little text differs materially from some of its predecessors in the same field in that emphasis is placed primarily on the symptomatology of disease. The interpretation of symptoms leads to a practical discussion of every phase of differential diagnosis.

The important and essential procedures at the bedside are stressed, and are presented in simple, lucid fashion.

The subject matter treated is amazingly extensive and comprehensive for so small a book. In connection with one or several outstanding symptoms, such as cyanosis or pallor, hyperpyrexia, convulsive seizures, hemorrhage of various forms, icterus, vomiting or diarrhea and many others, every conceivable disorder in any way related to the symptom and common to the given age level of the infant or child is discussed and clearly analyzed from the standpoint of differential diagnosis.

In such discussion, again, the primary and most likely disorders, or disorders related in any way to the symptom or symptoms, are exhaustively dealt with, along with at least mention of all other possibilities.

The size and nature of the text precluded any theoretical or academic discussion of disease, etiologically or otherwise, and it is wisely omitted, as it would certainly rob the book of its simplicity and lucidity and would probably tend to confuse rather than to guide the reader.

To the perplexed practitioner this type of book is a vade-mecum and a practical guide which for quick orientation and substantial useful help will prove far superior to many a ponderous text or handbook.

The author's style is excellent, and the diction is exceedingly clear and direct. One senses immediately that the book is written by a practitioner who has sensed in lively fashion the needs and shortcomings of his average fellow practitioner in pediatric practice.

DIE REFLEKTORISCHE SELBSTSTEUERUNG DES KREISLAUFES By PROF DR MED EBERHARD KOCH, Nauheim Paper Price, 18 marks Pp 234, with 44 illustrations Dresden Theodor Steinkopff, 1931

This monograph contains a well organized and critical summary of the present available information on the influence of the sensory nerves distributed to the heart, the aorta, the carotid sinus and other blood vessels, and on the reflex regulation of the heart itself and of the blood vessel musculature in health and in disease. That sensory nerves distributed to the walls of the ventricles and to the aorta contribute to cardiovascular reflex control has long been known. A number of years ago the work of a German physician, Hering, brought out the fact that there is an additional pronounced sensory region at the bifurcation of the carotids (the so-called carotid sinus) from which sensory impulses play a marked rôle in the cardiovascular reflexes. Later, though still fragmentary, information indicates that probably all blood vessels are supplied with afferents having important cardiovascular reflex function. The disturbance of these mechanisms in such pathologic conditions of the blood vessels as sclerosis or aneurysm is as yet imperfectly understood but constitutes an important problem of investigation in internal medicine.

The author handles the data, the problems and the theories in a clear and critical manner. The monograph is a distinct contribution to medicine and may be perused with profit by all students of medicine and physiology.

GNORRHEA IN THE MALE AND FEMALE A BOOK FOR PRACTITIONERS By PERCY S PELOUZE, M D, Associate in Urology and Assistant Genito-Urinary Surgeon at the University of Pennsylvania, Fellow of the Philadelphia College of Physicians Second edition, revised Cloth Price, \$5 50 net Pp 440, with 92 illustrations Philadelphia W B Saunders Company, 1931

This volume will interest every physician who comes in contact with the most prevalent of all diseases In this second edition of his popular work, Pelouze has added much to the scope of the discussion of gonorrhea, its complications and sequelae, but has not striven for encyclopedic comprehensiveness, nor sacrificed any of the direct simplicity that gives emphasis to his literary style On the basis of his own wide clinical experience, the author deplores the modern tendency to overtreat patients with gonorrhea He outlines with considerable clarity conservative and sane methods of management of the disease in its various stages, which have met with gratifying results in his own office and in clinical practice He does not offer empiric routines to be blindly followed, but makes a commendable effort to rationalize the methods of preference on the basis of the pathophysiologic principles that are involved

An important addition to the present edition is a section of fifty pages on gonorrhea in the female The text itself is sincere, vigorous and highly readable Occasionally the author relieves the seriousness of the problem with quiet and effective humor, such as "Wherefore it should be realized that the physician is but a child in the hands of a woman intent upon deception, and he should be willing to bow to the art with admiration for its finer points without greatly disturbing his scientific reasoning and skepticism about immaculate infection"

In the preface to the first edition, the author said, "publicly unspeakable and medically outcast, gonorrhea has limped through the ages a veritable 'nobody's child' It is a serious disease, and it needs serious attention" This splendid book gives the disease just that

NUTRITION AND DIET IN HEALTH AND DISEASE By JAMES S McLESTER Second edition Price, \$8 50 Pp 891 Philadelphia W B Saunders Company, 1931

This comprehensive study by McLester includes nutritional requirements for normal adults and children as well as diet in disease

The chapter on the normal diet emphasizes the fundamental considerations by which one must be governed for the proper selection of food Man's dietary needs are outlined in a base ration as suggested by E V McCollum

Infant feeding is discussed in a special chapter by Dr McKim Marriott of Washington University, St Louis The feeding of surgical patients is outlined by Dr Barney Brooke of Vanderbilt University, Nashville, Tenn

For the chapters on nutrition in disease, the literature of recent years has been gleaned for therapeutic and experimental diets These are reprinted in full or in part, with comments

This compilation of diets in disease is a great time-saver for the nutrition worker, and the extensive bibliographies are valuable

Menus and recipes are reprinted, which are helpful to use as patterns in planning diets to meet the requirement of the individual

The tables and charts of a general nature that are reprinted are adequate for calculation of diet

ENTSTEHUNG, ERKENNUNG UND BEHANDLUNG INNERER KRANKHEITEN By DR LUDOLF KREHL, Professor in Heidelberg Band II Die Erkennung innerer Krankheiten Paper Price, 12 80 marks Pp 172 Berlin F C W Vogel, 1931

This volume on diagnosis in internal medicine represents the second in Krehl's trilogy on the pathogenesis, diagnosis and treatment of internal diseases The term "diagnosis" is used in the broadest sense and therefore includes "Beurteilung,"

or the physician's considered judgment about the entire medical situation. What the latter amounts to in socialized Germany is brought out vividly, but dispassionately, in the first chapter. Those who are interested in so-called state medicine as it exists in Germany should read this chapter more than once. Krehl's entire philosophy of the place of medicine among the sciences and arts, his concepts of the physician's relation to the patient, his general advice as to the technic of the anamnesis and the synthesis of the data obtained, and a host of other details derived from the mature experience of this very human master of the Heidelberg Clinic make this chapter a work of art.

The remainder of the book is devoted to a systematic consideration of the general examination of the patient, infectious diseases and disturbances of the various systems. It is difficult to describe the material of these chapters because it is a mixture of high lights in physical diagnosis, laboratory methods, shrewd clinical intuition and delightful personal comments. It takes an unusually mature medical student to digest such stuff, but it is worth a little effort. The discussion of clinical disturbances of the circulation, respiration and formation of urine is particularly excellent. There are a few, but pertinent, references to the literature and frequent cross-references to the volume on pathologic physiology.

L'AEROPHAGIE By A. DOBROVICI Price, 10 francs Pp 31 Paris Gaston Doin, 1930

The author presents an excellent and logical treatise on aerophagia. He defines the condition as the swallowing of atmospheric air which may or may not be followed by belching. Physiologic aerophagia is discussed. Pathologic aerophagia is said to differ from the physiologic form either by the greater size of the air bubble in the stomach, or by the intolerance of air in a hypersensitive stomach and the dyspepsia and mechanical troubles that accompany distention of the digestive tube with air. The mechanisms of the unconscious swallowing of air are described.

Air is said to penetrate for varying distances in the digestive tube with the production of corresponding symptoms. 1 Eructation may be provoked simply by the accumulation of air partly swallowed into the pharynx. 2 Air penetrates more or less into the esophagus but does not reach the stomach and is rejected immediately through the mouth. 3 Air penetrates into the stomach, partly opening the cardia, and comes out afterward as eructations. 4 Air gets into the stomach in great quantities, is stored up there, causing distention, and is finally ejected by violent belching. 5 The swallowed air, after distending the stomach, passes through the pylorus and distends the intestines, and the act is completed when the air is expelled as flatus.

Treatment consists largely of explaining the mechanism of aerophagia to the patient. The necessity for his cooperation is emphasized.

BLUTKRANKHEITEN UND BLUTDIAGNOSTIK LEHRBUCH DER KLINISCHEN HAMATOLOGIE By OTTO NAEGELI Fifth revised edition Price, 86 marks Pp 704, with 104 illustrations Berlin Julius Springer, 1931

Naegeli's clinical hematology in its fifth revised German edition probably contains as comprehensive analyses and descriptions of the various technics of examination of the blood as any text now published. It includes much more detailed information concerning the various morphologic structures and physico-chemical constituents of the blood than any of the usual texts on laboratory technic. These matters concerning the various technical procedures, stains, morphology and variations of the erythrocytes and leukocytes are treated with attention to minute detail and a comprehensive bibliography. Many colored illustrations add greatly to the text. Extensive discussions are made, respectively, of the anemias, pernicious anemia, leukemia, pseudoleukemia and the changes of the blood with infectious diseases, helminthiasis, malignant tumors, poisons and blood toxins. Shorter sec-

tions are devoted to changes of the blood with paroxysmal hemoglobinuria and with diseases of the glands of internal secretion. Advanced students in hematology and clinicians, especially in internal medicine, will find this text valuable.

CHININ IN DER ALLGEMEINPRAXIS By DR MED FRITZ JOHANNESSEN
Paper Pp 232, with 3 illustrations Amsterdam Bureau Tot Bevoording
van Het Kinine-Gebruik, 1930

After a brief historical introduction, the author discusses briefly the pharmacognosy and chemistry of quinine as well as the fate of the drug after absorption. By far the greater part of the book is given over to a consideration of therapeutic uses of quinine in diseases other than malaria, which is discussed in less than a dozen pages. From the evidence presented, one may gain the impression that quinine is indicated in a great variety of infectious diseases (pulmonary diseases, pertussis, erysipelas, etc). However, surprisingly few authors who do not attribute their success to quinine or who have obtained untoward results are cited in the detailed discussion of many diseases which one rarely associates with quinine therapeutically. The author also cites numerous references to the use of the drug in disturbances of cardiac conduction, in the initiation of labor and in the treatment for varicose veins and hemorrhoids.

Quinidine is discussed in a separate chapter.

The book is indexed. The bibliographies contain 809 references.

LAGOUTTE By DANIEL CRITZMAN Paper Price, 25 francs Pp 235 Paris
Gaston Doin, 1931

This recent monograph on gout, given in French by a Roumanian who spent his professional life in France, has been revised posthumously by Jacques Forestier. It comes at a time when gout is receiving relatively little attention in the clinical literature of this country, owing, apparently, to the widespread belief that this is a rare disease.

The book contains the usual excellent clinical descriptions of the various stages and types of gout for which the French school is particularly noted. The principal theories of pathogenesis with the arguments pro and con are briefly discussed. In dealing with treatment, the author decries the modern tendency to proscribe all purine-containing foods, and he believes strongly in the more didactic methods of choosing the diet on the basis of experience. Medically, there is nothing new or successful. Those who have to deal with gout may well find much of value to them in this volume.

TABLES OF FOOD VALUES By ALICE V BRADLEY, B S, Supervisor and
Instructor of Nutrition and Health Education, State Teachers College, Santa
Barbara, Calif Price, \$2 Peoria, Ill The Manual Arts Press, 1931

This book of food tables should prove very useful to any one engaged in work on nutrition. It is written in a practical and concise form and includes recipes that enable the reader to know the formulas used in the computation of the foods listed.

The food tables are presented in the following manner: kind of food, measurement, weight, grams of protein, fat and carbohydrate, calories, mineral shares, vitamins, value as a source of bulk and acid and basic reactions.

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